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Article

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Echocardiographic Findings and Subsequent Risk of Native Valve Endocarditis

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Article

Echocardiographic Findings and Subsequent Risk of Native Valve Endocarditis

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Abstract: Background: The association of echocardiographic findings and subsequent risk of left-sided native valve endocarditis (LS-NVE) is undefined. The aim of this study was to determine if transthoracic echocardiographic (TTE) measurements are associated with the subsequent development of LS-NVE in patients without cardiac predisposing conditions. **Methods:** Institutional databases were evaluated for adults diagnosed with LS-NVE from 2008 to 2020. Patients with prosthetic valves, cardiovascular implantable electronic devices, intracardiac devices, injection drug use, and predisposing cardiac conditions were excluded. Only patients who had a TTE performed 6 months to 3 years before the development of LS-NVE were included as cases. Controls were patients within the same Mayo location with a TTE report and were matched in a 1:3 ratio according to age, gender, Charlson Comorbidity Index, and echocardiography date. **Results:** There were 148 cases and 431 matched controls. As compared to controls, IE cases had a higher prevalence of diabetes mellitus (46.6% vs. 30.4%) and chronic kidney disease (46.6% vs. 28.1%) ($p < 0.001$). Left ventricular outflow tract velocity ($p = 0.017$), left ventricular ejection fraction ($p = 0.018$), and E: e' ratio ($p = 0.050$) were associated with LS-NVE. **Conclusions:** Echocardiographic measurements were associated with subsequent LS-NVE development in this pilot study. A larger cohort of LS-NVE patients, however, is needed to validate these findings.

Keywords: endocarditis; echocardiography; native valve; left-sided; measurements; risk

1. Introduction

Infective endocarditis (IE) is a potentially life-threatening syndrome with an in-hospital mortality rate ~20% despite optimal medical and surgical management [1–3]. Echocardiography is an essential tool in the diagnosis of IE, but also in the identification of heart conditions that predispose to its development [4–7]. The designation of a predisposing heart condition is nonspecific for left-sided, native valve endocarditis (LS-NVE) and may include a myriad of congenital and acquired conditions such as congenital abnormalities, rheumatic heart disease, hypertrophic cardiomyopathy, bicuspid aortic valve or mitral valve prolapse [8–10,11–13].

Considering the: (i) nonspecific classification of predisposing cardiac conditions associated with the development of LS-NVE; (ii) fact that 40% of patients with NVE do not have a structural abnormality or valve damage prior to with the development of IE [14]; and (iii) evolution of technical

advances in echocardiography over recent years, it seems appropriate to evaluate echocardiography as a potential tool in assessing the likelihood of the subsequent development of LS-NVE. Thus, the primary objective of the current investigation was to determine whether transthoracic echocardiogram (TTE) measurements were associated with the subsequent development of LS-NVE in patients with no predisposing cardiac conditions.

2. Methods

A case-control study design was conducted. Cases and controls were adult (≥ 18 years) patients from Mayo Clinic sites (Rochester, Florida, Arizona, and the Health Systems) from 2008 to 2020. To determine the cases, institutional databases of patients with an initial diagnosis of LS-NVE were queried. Medical charts were reviewed, and IE cases were identified according to the modified Duke criteria [10], and categorized into either possible or definite LS-NVE. Only patients who had a TTE performed 6 months to 3 years before the development of IE were considered for study inclusion, and every individual was only included once. Controls were selected from a large retrospective cohort of adult patients with at least one TTE report over a similar period to that of the cases. Patients with prosthetic valves, cardiovascular implantable electronic devices (CIEDs), intracardiac devices, previous IE, injection drug use, and predisposing heart conditions (congenital abnormalities, rheumatic heart disease, hypertrophic cardiomyopathy, bicuspid aortic valve and mitral valve prolapse) were excluded among cases and controls.

Case and controls were matched using age, sex, Charlson Comorbidity Index (CCI) and date of echocardiogram. Our matching algorithm attempted to sample all LS-NVE cases and 3 times as many controls as cases, matching them exactly on sex and CCI category, and closely on age (± 3 years) and timing of echocardiography (± 1 year).

Details characterizing the degree of valve abnormality and other echocardiographic measurements, were then collected for both matched cases and controls. Clinical characteristics, medical history, procedures, and comorbid conditions (at the time of the patients' echocardiography) were also collected from the electronic health record. The CCI was calculated as described previously [15]. This study was approved by the Mayo Clinic Institutional Review Board and included only patients with institutional research authorization.

2.1. Echocardiographic measurements

A registered cardiac sonographer conducted the echocardiographic examination following the American Society of Echocardiography guidelines [16–18]. Data were extracted from the echocardiography reports for all patients. Mid-segmental linear measurements of the left ventricular (LV) internal systolic (LVISD) and diastolic dimensions (LVIDD), left ventricular posterior wall diastolic thickness (LVPWDT), and interventricular septum diastolic thickness (IVSDT) were performed in a parasternal long-axis view. LV ejection fraction (EF) was calculated using the modified Quinones equation or biplane method of disks (Simpson). For the hemodynamic measurements the velocity-time integral (VTI) and peak velocity of the left ventricular outflow tract (LVOT) were measured using pulsed wave Doppler in an apical long-axis or five-chamber view. LVOT diameter was measured using a parasternal long-axis view during systole. The LVOT cross-sectional area and VTI were multiplied to obtain the stroke volume [19]. Cardiac output was derived from (stroke volume \times heart rate) and then indexed according to the patient's body surface area. Transmitral flow was acquired using pulsed-wave Doppler for E-wave and tissue doppler for e'-wave. Both measurements were obtained from the septal side of the mitral annulus during the same heartbeat using a four-chamber view. The E wave to e' ratio was used to determine LV filling pressures. Native valvular regurgitation for the aortic and mitral valves was classified according to the American Society of Echocardiography guidelines into normal, trivial, mild, moderate, and severe [20].

2.2. Analytic plan and statistical analysis

To test for unadjusted associations between the case-control group and each of the clinical and echocardiographic variables, we used unmatched methods (e.g., Wilcoxon rank-sum tests, Pearson χ^2 tests) to avoid deletion of matched sets with partially missing data. However, the comparisons were also repeated on the matched sets using matched methods (univariable conditional logistic regression models) and checked for agreement. Results of these bivariate analyses were not used in selecting variables to include in the prognostic model of LS-NVE.

For echocardiographic data, measurements on 46 variables were collected. Of them, 20 were missing in >15% of patients and were therefore removed from further evaluation. Due to the paucity of severity categories, the ordinal variables for mitral and aortic stenosis were removed. In contrast, those for mitral and aortic regurgitation were retained but were dichotomized as presence (mild, moderate, or severe) or absence (none or trivial) to preserve degrees of freedom (df). Next, the remaining 24 echocardiographic variables were reduced to the 12 most clinically relevant ones. Lastly, we examined data redundancy among the remaining variables and removed two more variables: LV mass index (due to overlapping information with the other variables) and LVEDD (due to collinearity with LVESD). Hence, the final model was fitted with 10 echocardiographic variables (13 df), including 5 anatomical-related measures – IVSDT, LVESD, LVWDT, and mitral and aortic regurgitation – and 5 hemodynamic-related measures – LVEF, LVOT velocity, LV cardiac index, E: e' ratio, and AVSP velocity). Because significantly higher rates of chronic kidney disease and diabetes mellitus were found in the LS-NVE cases versus controls (despite matching on CCI), a post hoc analysis was conducted by repeating the original logistic regression with inclusion of these 2 additional covariates.

Continuous variables were modelled with 3-knot restricted cubic splines to assess the default assumption of nonlinearity. For those variables with little to no evidence of a nonlinear effect, the nonlinear terms were removed, and the variables were refitted as linear in the final model. To preserve the total sample size in the modelling despite missing data (the rate of missingness among echocardiographic variables ranged from 0% to 13.6%), multiple imputations were employed with 25 imputation sets based on predictive mean matching. Model estimates were depicted with partial effects plots to show how the predicted probabilities of IE changed over the range of observed values for each continuous variable. The relative contribution of variables to the model tested individually or as a group, was quantified with adjusted χ^2 statistics, whereby subtracting the degrees of freedom from the Wald partial χ^2 values, the contributions of variables can be compared on the same scale. The model was internally validated for discrimination and calibration using bootstrap resampling. Predictive discrimination was quantified by the C-statistic and other model indexes. At the same time, calibration was demonstrated with a smooth nonparametric calibration curve comparing predicted and observed probabilities of IE for both the original and bootstrapped models.

If not otherwise indicated, patient characteristics presented with median and interquartile ranges (IQR) for continuous variables and numbers and percentages for categorical or ordinal variables. A p value of <0.05 was considered statistically significant. Analyses were performed using the statistical programming language R, version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

Overall, a total of 579 patients were included in the analysis: 148 LS-NVE cases (124 definite [83.8%] and 24 possible) and 431 matched controls (Figure 1). The median age was 63.8 (IQR: 53.6 – 74.6) years, and 329 (56.8%) patients were males. The patients' race was predominantly white in both cases (91.8%) and controls (92.2%). LS-NVE cases had a higher prevalence of diabetes mellitus (46.6% vs. 30.4%) and chronic kidney disease (46.6% vs. 28.1%) when compared with controls ($p < 0.001$ for both comparisons). The median CCI score was 3 (IQR: 0–6) for cases and 2 (IQR: 0–6) for controls.

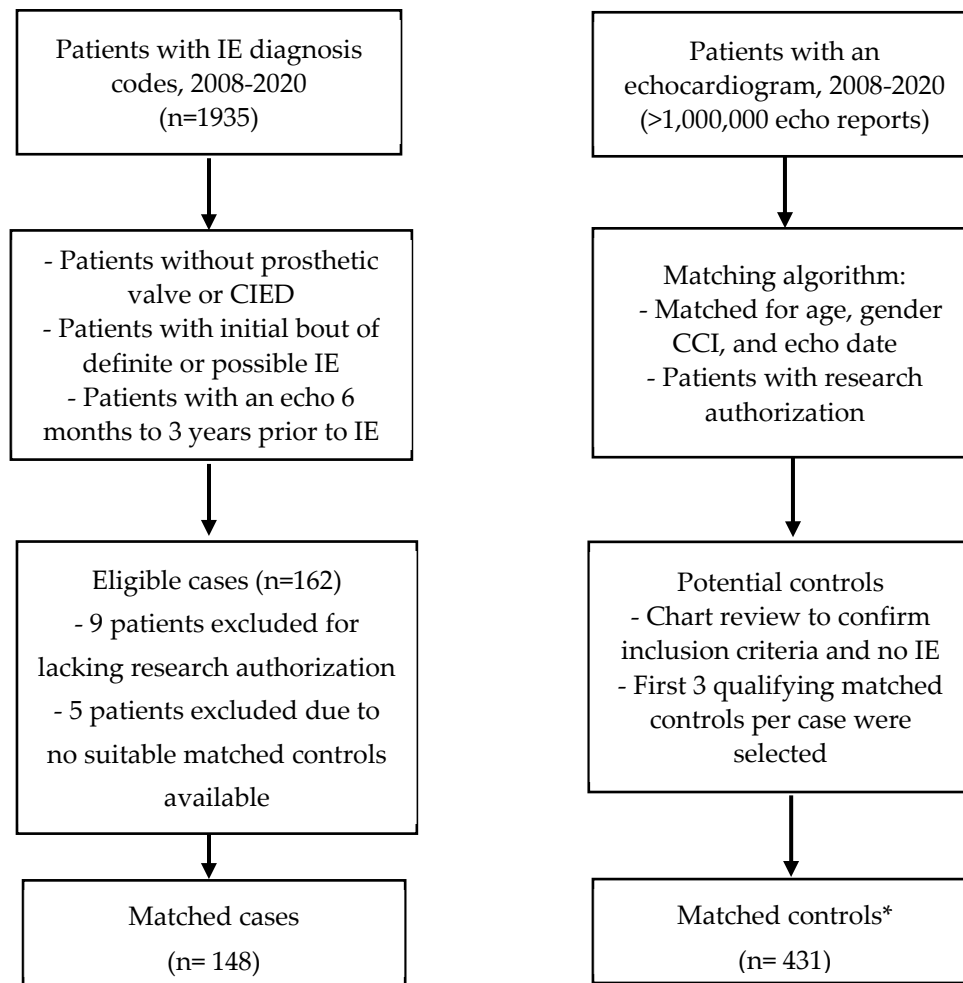


Figure 1. Selection flow chart demonstrating cases and controls. **Abbreviations:** IE, infective endocarditis; Echo, transthoracic echocardiography; CIED, cardiac implanted electronic device; CCI, Charlson comorbidity index. * Of the 148 matched sets, 137 (92.6%) included three matched controls per case, 9 (6.1%) had two controls, and 2 (1.4%) had only one suitable control.

Table 1. Demographics and Comorbid Conditions by IE Case Status.

Characteristic	N	Cases (N=148)	Controls (N=431)	p value
Year of echo	579	2015.9 (2011.7-2018.3)	2015.9 (2011.6-2018.4)	0.837 ¹
Male Gender	579	84 (56.8%)	245 (56.8%)	0.985 ²
Age at Time of Echo	579	63.7 (53.7-74.5)	63.8 (53.6-74.6)	0.905 ¹
Race: White	572	135 (91.8%)	392 (92.2%)	0.877 ²
Chronic Kidney Disease	579	69 (46.6%)	121 (28.1%)	< 0.001 ²
Hemodialysis	579	14 (9.5%)	1 (0.2%)	< 0.001 ²
Hypertrophic Cardiomyopathy	579	2 (1.4%)	3 (0.7%)	0.457 ²
Myocardial Infarction	579	27 (18.2%)	88 (20.4%)	0.567 ²
Hypertension	579	88 (59.5%)	238 (55.2%)	0.370 ²
Heart Failure	579	51 (34.5%)	139 (32.3%)	0.621 ²
Cerebral Stroke	579	3 (2.0%)	13 (3.0%)	0.526 ²
Diabetes Mellitus	579	69 (46.6%)	131 (30.4%)	< 0.001 ²
Charlson Index	579	3 (0-6)	2 (0-6)	0.421 ¹
Charlson Index Levels	579			0.819 ¹
0		43 (29.1%)	129 (29.9%)	

1	7 (4.7%)	21 (4.9%)
2	19 (12.8%)	56 (13.0%)
3	17 (11.5%)	47 (10.9%)
4-6	26 (17.6%)	75 (17.4%)
7-10	23 (15.5%)	68 (15.8%)
>10	13 (8.8%)	35 (8.1%)

Values represent median (quartile 1 to quartile 3) for continuous variables and frequency (percentage) for categorical variables. N is the number of non-missing values. P values are by ¹ Wilcoxon rank sum, ² Pearson χ^2 or ³ Fisher exact tests.

Echocardiographic variables that were routinely (i.e., in >80% of patients) measured in cases and controls are presented in Table 2. In these unadjusted analyses, anatomical echocardiographic measurements were different in patients with LS-NVE than those without IE, as evidenced by higher IVSDT, LVWDT and LV mass index ($p \leq 0.01$ for all comparisons). LS-NVE cases also exhibited different hemodynamics compared with controls based on higher LVOT velocity, LV cardiac index, mitral E and A wave, E: e' ratio, and AVSP velocity ($p \leq 0.002$ for all comparisons).

Table 2. Echocardiographic Measures by LS-NVE Case Status.

Measurement	N	Cases (N=148)	Controls (N=431)	p value
Heart Rate (bpm)	515	72.0 (63.0-81.8)	72.0 (61.0-83.0)	0.643 ¹
IVSDT (mm)	535	12.0 (10.0-13.0)	11.0 (10.0-12.0)	< 0.001 ¹
LVOT Systolic TVI (cm)	522	23.9 (20.8-27.0)	21.0 (18.0-24.0)	< 0.001 ¹
LVOT Velocity (m/sec)	526	1.2 (1.0-1.3)	1.0 (0.9-1.2)	< 0.001 ¹
LV Cardiac Output (l/min)	504	6.6 (5.3-7.9)	5.8 (5.1-6.9)	< 0.001 ¹
LV Cardiac Index (l/min/m ²)	502	3.3 (2.8-3.8)	3.0 (2.6-3.5)	0.002 ¹
LVEDD (mm)	547	49.0 (44.5-54.0)	48.0 (44.0-53.0)	0.280 ¹
LVESD (mm)	503	31.0 (28.0-35.0)	31.0 (28.0-35.0)	0.686 ¹
LV Mass (g)	531	200.0 (163.8-264.0)	181.0 (144.0-227.0)	0.004 ¹
LV Mass Index (g/m ²)	529	102.0 (83.0-122.2)	93.0 (77.0-114.0)	0.010 ¹
LVPWDT (mm)	535	11.0 (10.0-12.0)	10.0 (9.0-11.0)	< 0.001 ¹
LV Stroke Volume (ml)	516	94.5 (79.0-108.0)	82.0 (69.0-99.0)	< 0.001 ¹
LV Systolic Stroke Volume Index (ml/m ²)	509	47.0 (40.0-53.0)	43.0 (37.0-49.0)	< 0.001 ¹
MV E-Wave Peak Velocity (m/sec)	526	0.9 (0.7-1.1)	0.8 (0.6-1.0)	< 0.001 ¹
MV A-Wave Peak Velocity (m/sec)	465	0.9 (0.7-1.1)	0.7 (0.6-0.9)	< 0.001 ¹
MV Deceleration Time (msec)	486	210.5 (177.5-265.5)	195.5 (167.8-227.0)	< 0.001 ¹
MV Annulus e' Velocity (m/sec)	523	0.1 (0.1-0.1)	0.1 (0.1-0.1)	0.195 ¹
MV E: e'	512	13.8 (10.0-18.0)	11.1 (8.2-16.0)	< 0.001 ¹
Aortic Stenosis	565			0.670 ²
none		132 (90.4%)	391 (93.3%)	
trivial		2 (1.4%)	4 (1.0%)	
mild		7 (4.8%)	7 (1.7%)	
moderate		4 (2.7%)	7 (1.7%)	
severe		1 (0.7%)	10 (2.4%)	
Aortic Regurgitation	565			0.552 ²
none		85 (58.2%)	258 (61.6%)	
trivial		39 (26.7%)	93 (22.2%)	
mild		14 (9.6%)	52 (12.4%)	
moderate		6 (4.1%)	15 (3.6%)	

severe		2 (1.4%)	1 (0.2%)	
Mitral Stenosis	570			0.032 ²
none		141 (95.9%)	420 (99.3%)	
trivial		1 (0.7%)	0 (0.0%)	
mild		5 (3.4%)	1 (0.2%)	
moderate		0 (0.0%)	2 (0.5%)	
Mitral Regurgitation	570			0.547 ²
none		19 (12.9%)	38 (9.0%)	
trivial		78 (53.1%)	229 (54.1%)	
mild		32 (21.8%)	102 (24.1%)	
moderate		12 (8.2%)	46 (10.9%)	
severe		6 (4.1%)	8 (1.9%)	
AVA by Velocity (cm ²)	469	2.8 (2.2-3.5)	3.0 (2.3-3.5)	0.170 ¹
AVSP Velocity (m/sec)	484	1.5 (1.4-2.0)	1.4 (1.2-1.7)	< 0.001 ¹
AV Systolic TVI (cm)	447	33.4 (27.0-43.0)	28.0 (23.1-34.0)	< 0.001 ¹
LVOT Systolic Diameter (cm)	525	2.2 (2.1-2.4)	2.2 (2.1-2.4)	0.913 ¹
LVEF (%)	549	62.0 (58.0-67.0)	61.0 (56.0-65.0)	0.024 ¹

Values represent median (quartile 1 to quartile 3) for continuous variables and frequency (percentage) for ordinal variables. N is the number of non-missing values. P values are by ¹ Wilcoxon rank sum or ² proportion trend tests. Abbreviations: LS-NVE, left sided native valve endocarditis; IVSDT, interventricular septum diastolic thickness; LVOT, left ventricular outflow tract; TVI, time velocity integral; LV, left ventricular; LVEDD, LV end diastolic dimension; LVESD, LV end systolic dimension; LVPWDT, LV posterior wall diastolic thickness; MV, mitral valve; AV, aortic valve; AVA, AV area; AVSP, AV systolic peak; LVEF, LV ejection fraction.

A multivariable conditional logistic regression model was developed to determine the association of anatomical and hemodynamic measurements with the risk of LS-NVE. The selection of variables to be included in the model was based on a priori knowledge and data reduction methods blinded to the case-control group, resulting in 10 variables selected for inclusion (Table 3). Ranked by importance according to their adjusted χ^2 values from the model (Figure 2), LVOT velocity ($p=0.017$), and LVEF ($p=0.018$) and E: e' ($p=0.050$) were significantly associated with LS-NVE. When re-expressed in terms of grouped variables, the hemodynamic-related variables had a stronger contribution to the model (corrected $\chi^2=31.7$; $p<0.001$) than the anatomical landmark-related variables (corrected $\chi^2=11.1$; $p=0.086$). A partial effects plot for the continuous variables in the final model is presented in Figure 3.

Table 3. Adjusted Odds Ratios and 95% Confidence Intervals.

Variable	Contrast	Odds Ratio (95% Confidence Interval)	Test Statistic
IVSDT	12 : 10	1.13 (0.82 - 1.56)	$\chi^2=3.48$, $P=0.176$
LVESD	35 : 28	1.38 (0.95 - 2.01)	$\chi^2=2.81$, $P=0.094$
LVEF	46 : 61	0.34 (0.16 - 0.73)	$\chi^2=8.02$, $P=0.018$
	69 : 61	1.07 (0.67 - 1.71)	
LVPWDT	12 : 9	1.35 (0.83 - 2.20)	$\chi^2=1.43$, $P=0.232$
Aortic Regurgitation	Mild to Severe : None or Trivial	0.71 (0.39 - 1.28)	$\chi^2=1.32$, $P=0.250$
Mitral Regurgitation	Mild to Severe : None or Trivial	0.96 (0.58 - 1.58)	$\chi^2=0.03$, $P=0.868$
LVOT Velocity	0.9 : 1.1	0.51 (0.32 - 0.82)	$\chi^2=8.20$, $P=0.017$
	1.4 : 1.1	1.20 (0.75 - 1.91)	

LV Cardiac Index	3.6 : 2.6	1.05 (0.78 - 1.43)	$\chi^2_1=0.11$, P=0.742
MV E: e'	16.7 : 8.6	1.42 (1.00 - 2.02)	$\chi^2_1=3.85$, P=0.050
AVSP Velocity	1.7 : 1.2	1.08 (0.84 - 1.40)	$\chi^2_1=0.37$, P=0.543

For all continuous variables except LVOT and LVEF, the odds ratios represent an interquartile increase in that variable (i.e., an increase from the 25th to the 75th percentile). For LVOT and LVEF, which appear to be non-monotonically related with the outcome (see Figure 3), odds ratios are calculated at 2 data points compared with the median (i.e., 50th percentile) to represent the effects of having an extreme low value (10th percentile) and an extreme high value (90th percentile). As IVSDT, LVOT and LVEF each showed evidence of nonlinearity, these variables were modeled with regression splines and their overall tests of association are based on 2 degrees of freedom. Abbreviations: IVSDT, interventricular septum diastolic thickness; LVOT, left ventricular outflow tract; LV, left ventricular; LVESD, LV end systolic dimension; LVPWDT, LV posterior wall diastolic thickness; MV, mitral valve; AVSP, aortic valve systolic peak; LVEF, LV ejection fraction.

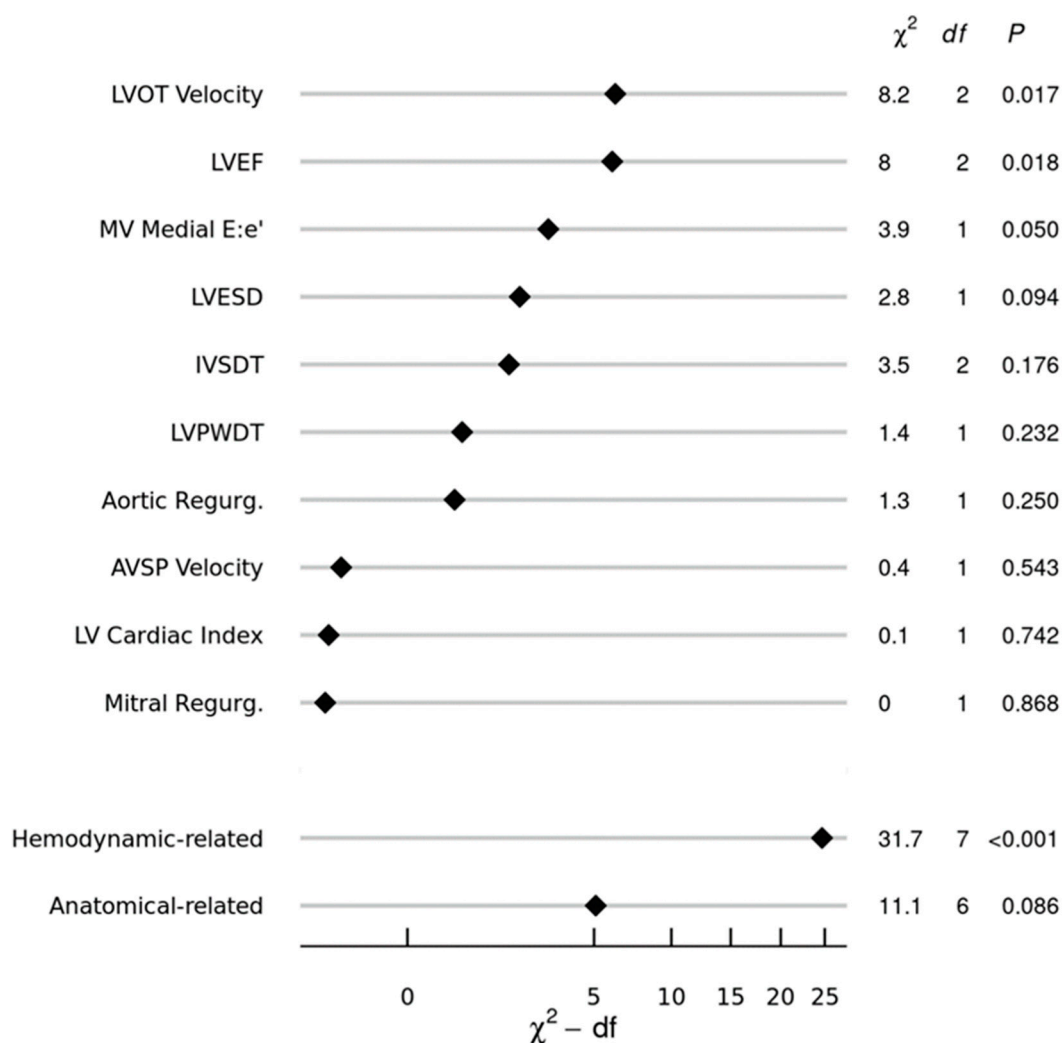


Figure 2. Relative Importance of Individual and Grouped Echocardiographic Variables. Abbreviations: IVSDT, interventricular septum diastolic thickness; LV, Left ventricular; LVEF, LV ejection fraction; LVESD, LV end-systolic dimension; LVPWDT, LV posterior wall diastolic thickness; AVSP, aortic valve systolic peak velocity; LVOT, LV outflow tract; MV, mitral valve.

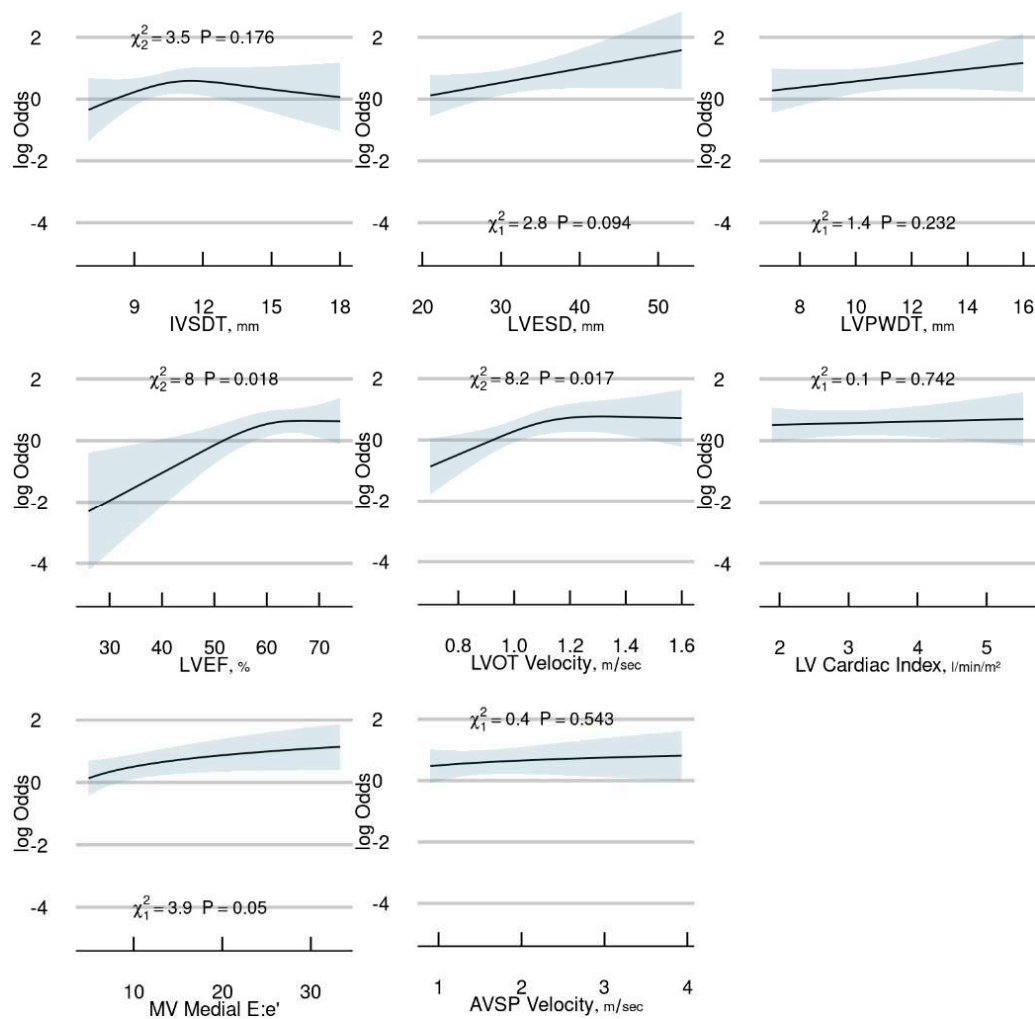


Figure 3. Partial Effects Plot for Continuous Variables. Abbreviations: IVSDT, interventricular septum diastolic thickness; LV, Left ventricular; LVEF, LV ejection fraction; LVESD, LV end-systolic dimension; LVPWDT, LV posterior wall diastolic thickness; AVSP, aortic valve systolic peak; LVOT, LV outflow tract; MV, mitral valve.

The bias-corrected C statistic of the model was 0.67, indicating modest discrimination in predicting LS-NVE for an individual patient. Using the bootstrap method to internally validate and calibrate the model, the estimated slope shrinkage factor of 0.79 suggested minor overfitting. The bias-corrected calibration curve presented in Figure 4 demonstrates that the model is generally well calibrated across the risk range, except for higher risk profiles where the model tends to underestimate the probability of IE. Model-based predictions of LS-NVE (in the matched sample), as estimated by the mathematical formula in Supplemental Figure S1, are illustrated for ten hypothetical patients in Supplemental Table S1.

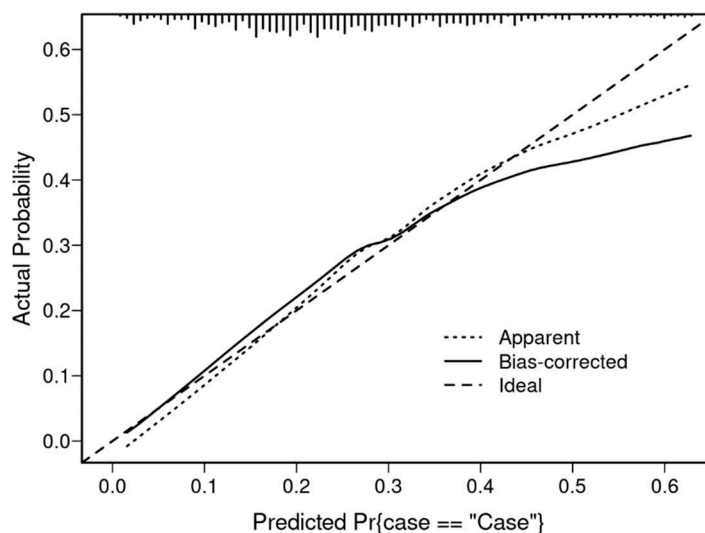


Figure 4. Bias corrected calibration curve.

A secondary analysis in which terms for diabetes mellitus and chronic kidney disease were added to the original model yielded similar findings concerning echocardiographic variables, except for E: e' which was no longer significant (Supplemental Figures S2 and S3).

4. Discussion

This is the first study to evaluate multiple specific TTE measurements and determine whether they were associated the subsequent development of LS-NVE in patients with no known cardiac predisposing conditions. Our primary finding was that increased peak LVOT velocity and LVEF were hemodynamic echocardiographic measurements associated with the subsequent development of LS-NVE. It is conceivable that increased LV pressures and velocities could be operative in IE predisposition by causing substantial turbulence that could create a substrate for endocardial injury as highlighted in an experimental model highlighting a “damage-induced” pathway [12]. Nevertheless, it is important to mention that there is limited clinical application for these results, future larger scale studies should be performed to assess the relevance of our findings.

It has been estimated that more than 800,000 individuals are at a high risk of IE in the United States alone [25]. Nevertheless, there is not a clear NVE diagnostic scheme for patients with ‘formally’ structural normal heart valve conditions. Thus, by implementing our analysis, which included an in-depth characterization of cardiac disease with the use of quantitative echocardiographic measurements, but also recognizing clinical parameters, may provide the most useful foundation for a future strategy in identifying patients who may have an increased risk of IE.

We did not detect an association between the degree of mitral and aortic regurgitation and subsequent development of IE in our multivariable model. Previous work has shown that valvular dysfunction is associated with IE, however, in contrast to our study, they included patients with predisposing cardiac conditions. Namely, the degree of mitral regurgitation, could be a risk factor associated with the development of IE in patients with mitral valve prolapse [28]. Of note, the inclusion of stenotic lesions of the mitral and aortic valves in our multivariable model was not possible due to their limited prevalence in our study cohort.

Diabetes mellitus and chronic kidney disease were identified as predisposing comorbidities for the development of LS-NVE in the current investigation. Diabetes mellitus is well recognized as an independent risk factor associated with IE; these patients can have an impaired immune response, delayed healing, reduced tissue vascularization and endothelial dysfunction [21]. Chronic kidney disease patients, particularly those with end-stage renal disease receiving hemodialysis, are at a significantly higher risk of developing IE when compared to the general population due to a higher prevalence of bacteremia related to vascular access and because of uremia-related impaired immune

response [22,23]. In addition, both diabetes mellitus and chronic kidney disease have a higher rate of *S. aureus* colonization than the general population, and hence, an increased risk of *S. aureus* bacteremia, which consequently increases the risk of IE [24].

5. Limitations

Our study is based on a retrospective case-control design and is subject to inherent limitations. First, given our relatively modest sample size, the large number of echocardiographic variables available posed statistical challenges with model development, therefore, we used data reduction based on clinical sensibility, lack of redundancy, and data completeness. Second, the retrospective nature of this study precluded the acquisition of complete echocardiographic measurements in all patients; however, a strength of our modeling approach is that only parameters that were routinely available (i.e., measured in $\geq 80\%$ of the subjects) were included. Third, this study was conducted at a tertiary medical center which may have introduced selection and referral bias. Fourth, our population was composed of adult patients who were predominantly white and of northern European descent; thus, the generalizability of our results to other populations is uncertain. Finally, despite the association of peak LVOT velocity and LVEF measurements with the development of IE, the differences between the compared study groups were small and are not applicable in clinical practice given that they can be confounded by the inherent interobserver variability of TTE. However, it is crucial to recognize the potential value and opportunity this presents for conducting a larger-scale investigation to assess the importance of these findings. A larger sample size would enhance statistical power, allowing for more precise estimation of effect sizes and detection of smaller, yet clinically relevant, effects.

6. Conclusions

Specific hemodynamic echocardiographic measurements were independently associated with LS-NVE in patients with no known predisposing cardiac conditions in our preliminary investigation. These measurements underpin the importance of alterations in hemodynamic function in predisposing to NVE. While our results demonstrated an association of echocardiographic measures with the subsequent development of IE, further investigation is needed to validate these preliminary findings.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org, Table S1: Model-Predicted Risk of LS-NVE for 10 Hypothetical Patients, Figure S1: Logistic Regression Equation for Risk of LS-NVE, Figure S2. Secondary model Relative Importance of Individual and Grouped Predictor Variables, Figure S3. Conditional versus Unconditional Logistic Regression.

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