Echocardiographic Hemodynamic Burden Parameters Predict Mitral Regurgitation Severity

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Abstract

Background Mitral regurgitation (MR) is the most common valvular heart disease. Since delaying severe MR treatment can lead to left ventricular dysfunction, early MR diagnosis is crucial. Echocardiography is the first-line diagnostic modality for evaluating MR severity. Transesophageal echocardiography (TEE) and newer imaging modalities like cardiac magnetic resonance imaging (CMR) are growing to be used due to the pitfalls of transthoracic echocardiography (TTE). However, these newer modalities have disadvantages, such as high cost, requiring highly-skilled operators, and expensive devices, that make them not widely available in developing countries. We evaluated novel TTE-derived hemodynamic burden parameters of MR to estimate and classify MR severity more precisely. **Methods** We prospectively enrolled 93 patients with primary MR from April 2022 to August 2022. We obtained the baseline characteristics and the following TTE parameters: mitral valve (MV) velocity-time integral (VTI), left ventricular outlet (LVOT) diameter (D), LVOT VTI, and mitral valve annulus (MVA) diameter. The statistical analysis was performed using SPSS. **Results** A total of 93 MR patients with a median (interquartile range) age of 59.00 (50.50-65.00) were recruited, of whom 38 (40.9%) were female. Of the 93 patients, 29 (31.2%), 29 (31.2%), and 35 (37.6%) were classified into mild, moderate, and severe MR, respectively. The four parameters of MVVTI/LVOTVTI, MVAVTI-index (i), MVAVTI/LVOTDVTI, and E velocity-LA area-i were shown to be significantly different among mild, moderate, and severe MR groups (p-values <0.001). Spearman's correlation test indicated that MVVTI/LVOTVTI, MVAVTI-i, MVAVTI/LVOTDVTI, and E velocity-LA area-i were highly and significantly correlated with MR severity classification with correlation coefficients of 0.776, 0.672, 0.822, and 0.698, respectively (p-values <0.001). The ROC-curve analysis demonstrated that all parameters were significantly accurate predictors of severe MR diagnosis. The area under curve (AUC) of the MVVTI/LVOTVTI, MVAVTI-i, MVAVTI/LVOTDVTI, and E velocity-LA area-i were 0.976, 0.975, 0.986, and 0.895, respectively (p-values <0.001) **Conclusion** We introduced novel TTE-derived MR hemodynamic burden indices. These indices were highly correlated with MR severity. Furthermore, they were significantly accurate predictors of severe MR. Proposing such new indices to older measures may improve their predictive value.

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Running title: Mitral Regurgitation Hemodynamic Burden

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Ethics approval and consent to participate

The Ethics committee of the Rajaie Cardiovascular Medical and Research Center, Iran University of Medical Sciences, Tehran, Iran, approved the study. The goal of this study was explained to the patients, and the informed written constant was obtained prior to echocardiography. Informed written consent was obtained from all participants. In all stages of the study, we adhered to the statement of Helsinki.

Consent for publication

Not applicable.

Data availability

Data are available upon reasonable request.

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Conflict of Interests

The authors declare no conflict of interest.

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Abstract

Background

Mitral regurgitation (MR) is the most common valvular heart disease. Since delaying severe MR treatment can lead to left ventricular dysfunction, early MR diagnosis is crucial. Echocardiography is the first-line diagnostic modality for evaluating MR severity. Transesophageal echocardiography (TEE) and newer imaging modalities like cardiac magnetic resonance imaging (CMR) are growing to be used due to the pitfalls of transthoracic echocardiography (TTE). However, these newer modalities have disadvantages, such as high cost, requiring highly-skilled operators, and expensive devices, that make them not widely available in developing countries.

We evaluated novel TTE-derived hemodynamic burden parameters of MR to estimate and classify MR severity more precisely.

Methods

We prospectively enrolled 93 patients with primary MR from April 2022 to August 2022. We obtained the baseline characteristics and the following TTE parameters: mitral valve (MV) velocity-time integral (VTI),

left ventricular outlet (LVOT) diameter (D), LVOT VTI, and mitral valve annulus (MVA) diameter. The statistical analysis was performed using SPSS.

Results

A total of 93 MR patients with a median (interquartile range) age of 59.00 (50.50-65.00) were recruited, of whom 38 (40.9%) were female. Of the 93 patients, 29 (31.2%), 29 (31.2%), and 35 (37.6%) were classified into mild, moderate, and severe MR, respectively. The four parameters of MVVTI/LVOTVTI, MVAVTI-index (i), MVAVTI/LVOTDVTI, and E velocity-LA area-i were shown to be significantly different among mild, moderate, and severe MR groups (p-values <0.001). Spearman's correlation test indicated that MVVTI/LVOTVTI, MVAVTI-i, MVAVTI/LVOTDVTI, and E velocity-LA area-i were highly and significantly correlated with MR severity classification with correlation coefficients of 0.776, 0.672, 0.822, and 0.698, respectively (p-values <0.001). The ROC-curve analysis demonstrated that all parameters were significantly accurate predictors of severe MR diagnosis. The area under curve (AUC) of the MVVTI/LVOTVTI, MVAVTI-i, MVAVTI/LVOTDVTI, and E velocity-LA area-i were 0.976, 0.975, 0.986, and 0.895, respectively (p-values <0.001)

Conclusion

We introduced novel TTE-derived MR hemodynamic burden indices. These indices were highly correlated with MR severity. Furthermore, they were significantly accurate predictors of severe MR. Proposing such new indices to older measures may improve their predictive value.

Keywords: Mitral Regurgitation, transthoracic echocardiography, hemodynamic burden, mitral valve annulus, velocity-time integral.

Introduction

Mitral regurgitation (MR) stands as the most common valvular heart disease in developed countries and is a prevalent medical condition in the elderly, whereas 10% of patients aged 75 are affected (1). MR is categorized as primary and functional types founded on the straight or indirect engagement of mitral valve constituents (2). Several medical and interventional therapies have been proposed for patients with MR. However, interventional approaches, including surgery, valvular replacement therapy, and trans-catheter mitral valve repair, are first-line treatments for patients with severe MR (3, 4). Patients with MR can present with asymptomatic to severe forms. It is essential to accurately determine MR severity and schedule the time of surgery, whereas delaying the surgery of severe MR patients can result in left ventricular dysfunction (5). Noteworthy, reduced left ventricular ejection fraction also indicates a bad prognosis for patients with MR (6). Therefore, the time of accurate staging of MR severity is the state-of-art to prevent the deterioration of patients with MR.

Echocardiography is the commonly used and first-line diagnostic method for evaluating MR severity (7). However, for a more accurate determination of MR severity, using the combined imaging methods in the setting of quantitative, semi-quantitative, and qualitative modalities is recommended (8). Advanced imaging modalities like cardiac magnetic resonance imaging (CMR) and computed tomography (CT) scan are gradually increasing recently due to the providing complementary data and suboptimal findings of echocardiography, especially in patients requiring additional evidence for making clinical decisions (9). Besides, transesophageal echocardiography (TEE) has become widely used within the last two decades and has its own disadvantages, such as skill-dependent procedures, malfunction of the probe, and complications related to the long-term sedation of patients that make it inappropriate first-line modality (10). However, these recently developed modalities have disadvantages, such as high cost, requiring highly-skilled operators, and expensive devices, that make them not widely available in developing countries. Therefore, considering new parameters on the findings of traditional imaging modalities are essential to covering the gaps in these modalities and providing a more accurate staging of the MR severity. Here, we evaluated new echocardiographic parameters to assist more precise estimations of mitral regurgitation severity and to provide an accurate method to classify MR severity in transthoracic echocardiography (TTE).

Methods

Participants

This prospective study included 93 patients with MR referred to our tertiary center to investigate the severity of MR from April 2022 to August 2022. The inclusion criteria were patients diagnosed with primary MR using the two-dimensional (2D) TEE without any concomitant valvular diseases at different severity without age restriction. Exclusion criteria are pregnancy, patients with intracardiac shunt, history of mitral valve surgery or replacement, and hypertrophic cardiomyopathy. The manuscript was written in accordance with the STROBE checklist (11).

Echocardiographic Information

Echocardiographic was carried out using 2D TEE (X8-2T probe, Philips echocardiography machine EPIQ -7, Philips Healthcare, Andover, MA, USA) to determine MR severity. MR was confirmed by color flow and Doppler indices according to the MR severity criteria. MR severity criteria are as follows: 1. Mild: Vena Contracta width (VCW) [?] 0.3 cm, proximal isovelocity surface area (PISA) radius absent or [?] 0.3 cm, Normal LV and LA size, Effective Regurgitant Orifice Area (EROA) $<$ 0.2 cm (for primary MR), Regurgitant Volume (RVol) $<$ 30 ml, Regurgitant Fraction (RF) $<$ 30%. 2. Moderate: intermediate values and EROA 0.20-0.39 cm(for primary MR), RVol 30-59 ml, RF 30-49%. 3. Severe: Flail leaflet, VCW [?] 0.7 cm, PISA radius [?] 1.0 cm, EROA [?] 0.4 cm, RVol [?] 60 ml, RF [?] 50% (8).

Then patients underwent 2D TTE (X8-2T probe, Philips echocardiography machine EPIQ -7, Philips Healthcare, Andover, MA, USA), and a comprehensive examination of the mitral valve and mitral regurgitation at standard imaging views was conducted. The demographic characteristics of patients, including sex and age, and the echocardiographic parameters of hemodynamic burden, including mitral valve velocity-time integral (VTI), left ventricular outlet (LVOT) diameter, LVOTVTI, mitral valve annulus (MVA) diameter, were acquired. The parameters investigating the hemodynamic burden of MR are listed below:

1. MVVTI/LVOTVTI: $\frac{\textbf{Mitral valve velocity}-\textbf{time integral (MV VTI)}}{\textbf{Left ventricle outlet velocity}-\textbf{time integral (LVOT VTI)}}$ MVVTI was measured with pulse Doppler at MV annulus in A4C view. LVOTVTI was measured with pulse Doppler at LVOT in A5C view.
2. MVAVTI-i: $\frac{\text{mitral valve annulus diameter} \quad \textbf{Mitral valve velocity}-\textbf{time integral}}{\text{BSA}}$ MVA was measured in A4C view just after the beginning of the mitral leaflet closing. i = indexed for body surface area (BSA).
3. MVAVTI/LVOTDVTI: $\frac{\text{Mitral valve annulus diameter} \quad \text{MV VTI}}{\textbf{LVOT D}*\textbf{LVOT VTI}}$ LVOTD was measured at PLAX view in mid-systole.
4. E velocity-LA area-i: E velocity **left atrium (LA) area** / BSA E velocity was measured at the mitral leaflet tip in diastole. LA area was measured in A4C view at its largest area. i = indexed for BSA.

Ethical consideration

The Ethics committee of the Rajaie Cardiovascular Medical and Research Center, Iran University of Medical Sciences, Tehran, Iran, approved the study. The goal of this study was explained to the patients, and the informed written constant was obtained prior to echocardiography. Informed written consent was obtained from all participants. In all stages of the study, we adhered to the statement of Helsinki (12).

Statistical analysis

The statistical analysis was performed using IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, N.Y., USA). The quantitative and qualitative variables are shown as mean ± standard deviation (SD) and absolute number (or percentage), respectively. One-sample Kolmogorov-Smirnov test was used to investigate the normal distribution of parameters. One-way ANOVA test is used to compare the means of continuous parameters and the independent sample Kruskal-Wallis test for nonparametric variables. Spearman and Pearson's correlation is applied for nonparametric and parametric variables, respectively, to explore the correlation between different variables. Finally, a receiver operator characteristic (ROC) curve analysis of the echocardiographic parameters and measurement of the area under the curve (AUC) was performed. A p-value less than 0.05 was considered statistically significant.

Results

A total of 93 MR patients with a median (IQR) age of 59.00 (50.50-65.00) were recruited for the study, of whom 38 (40.9%) were female. Of the 93 patients, 29 (31.2%), 29 (31.2%), and 35 (37.6%) were classified into mild, moderate, and severe MR, respectively. All variables were non-normally distributed; thus, the nonparametric tests were utilized.

Comparison of the Echocardiographic Parameters between MR Severity Groups

All four parameters of MVVTI/LVOTVTI, MVAVTI-i, MVAVTI/LVOTDVTI, and E velocity-LA area-i were shown to be significantly different among mild, moderate, and severe MR groups (all p-values <0.001) (Table 1). A pairwise comparison of the MR groups yielded by Bonferroni correction was performed. In all four parameters, there was a significant difference between the median (IQR) values of mild and severe MR groups (all p-values <0.001) and between moderate and severe MR groups (all p-values <0.001). However, no significant difference was observed between the mild and moderate MR groups in all four parameters (Table 1) (p-value for MVVTI/LVOTVTI = 0.538, MVAVTI-i = 1.000, MVAVTI/LVOTDVTI = 0.137, and E velocity-LA area-i = 0.069).

Correlation of the Echocardiographic Parameters and the MR Classification

Spearman's correlation test indicated that MVVTI/LVOTVTI, MVAVTI-i, MVAVTI/LVOTDVTI, and E velocity-LA area-i were highly and significantly correlated with MR severity classification with correlation coefficients of 0.776, 0.672, 0.822, and 0.698, respectively (all p-values <0.001) (Table 2).

ROC Curve Analysis for Diagnostic Accuracy

The ROC-curve analysis demonstrated that all parameters were significantly accurate predictors of severe MR diagnosis. The AUC of the MVVTI/LVOTVTI, MVAVTI-i, MVAVTI/LVOTDVTI, and E velocity-LA area-i were 0.976, 0.975, 0.986, and 0.895, respectively (all p-values <0.001) (Table 3). The ROC curve is represented in Figure 1.

Discussion

Although some mild forms of MR can be present in healthy individuals, severe forms can result in serious problems (13). MR in a moderate to severe form is the most frequent valvular disease in the USA (1) and the second most surgery-required valvular complication in Europe (14).

MR can occur due to various causes and mechanisms. The etiologies are classified either as ischemic -a consequence of coronary disease- or otherwise non-ischemic. Mechanisms are divided into two groups: organic (primary) with an intrinsic valvular lesion which contains degenerative mitral valve disease as the most frequent mechanism of MR (60–70%) and functional (secondary) with a structurally normal but deformed mitral valve as a result of left ventricular remodeling (13). The primary mechanism is subclassified based on the leaflet movement, as a normal movement represents class I, and excessive or restricted movement is classified as class II and III, respectively (15).

After suspicion is raised about the MR through clinical presentations and physical examinations like a displaced apical impulse, systolic murmur, third heart sound, early diastolic rumble, and atrial fibrillation, clinical and paraclinical studies to investigate the MR should be pursued. Signs and symptoms of heart failure (HF) and severe MR should be looked for in the clinical assessment, although they are not specific to MR (16). TTE is usually the first paraclinical modality to assess regurgitation. Gathering data on causes, mechanisms, severity, and the impact of regurgitation must be followed (8, 13).

Chronic volume overload of the left ventricle can happen as a consequence of a neglected MR. this can lead to increased left atrial pressure, increased pulmonary venous pressure, pulmonary edema, and subsequently, right-sided HF. Severe MR is associated with a 5-year mortality of 50%. Facing outcomes of the MR, like HF, will be inevitable for the survivors, as it happens for approximately 90% of them (17). MR independently increases the burden of other cardiac conditions, as it increases the mortality in patients with severe systolic HF (18).

According to the management guidelines, surgery is introduced as the only definite treatment (19). The severity of the MR increases the necessity of the surgery, even in the presence of advanced HF or ventricular dysfunction (20). This shows the importance of precise quantification of the severity. Paraclinical imaging methods, along with criteria, are developing to achieve an optimal introduction of patients to surgery (8). Other factors, like the cause and mechanism of the MR, affect the decision for surgical correction as well (15).

Different features should be gathered through echocardiography to determine the regurgitation severity, which can be divided into four groups. To begin with, the structure of the valve, leaflets, and mechanical findings should be described. It can range from normal leaflets to severely damaged valves with lesions like large perforations or flail leaflets. The size of the left atrium and ventricle should also be measured. Secondly, a qualitative Doppler assessment of color flow jet area, flow convergence, and Continuous Wave Doppler (CWD) jet is required.

Further, semi-quantitative data like VCW, pulmonary vein flow, and mitral inflow must be gathered. Last but not least, quantitative measures are reported to clarify MR severity. These factors include the EROA, a basic measure representing the regurgitation severity, and RVol, which can help estimate the overload burden and the RF. Values of EROA and RVol are the strongest predictors of the outcome. While data from these four groups should be assessed together, some features can individually specify the lesion severity (8).

Three methods are available to calculate the quantitative measures of MR severity: The flow convergence method (PISA method), the Quantitative volumetric method, and the Quantitative pulsed Doppler method. All these methods have some common components (Rvol, RF, and EROA). RVol is determined as the blood volume which regurgitates in one beat. RF is defined as RVol divided by the stroke volume through the regurgitant valve, and the EROA is calculated as the RVol divided by the VTI of the regurgitation jet. These quantitative methods have some complexities. An expert operator is required to assess the primary measures. Because, for example, in some methods assessing the mitral annulus diameter is required, which is hard to obtain, or unless an exact radius value is prepared in the PISA method, the EROA would be largely miscalculated (8).

In cases where TTE reports suboptimal results, TEE can be helpful (8). In TEE, the proximity of the probe to the mitral valve with a higher spatial resolution can help to recognize the MR severity more accurately (3). It also can give a better perspective on the exact location of the deficit, which can facilitate further interventions and surgeries (9, 18). TEE is useful when more exact quantification of the measures is required, for instance, jet color characteristics like VCW, VCA, and PISA radius. TEE can also more accurately evaluate the pulmonary veins and potential reverse flow (18). However, TEE is a semi-invasive method that relies on geometric assumptions and is not generally available, making TTE the suitable method for preliminary and serial studies of MR (9). TEE demonstrates the color jets larger than TTE, and as it is done under sedation, because of the altered hemodynamic status and particularly decreased blood pressure, the MR severity might be underestimated (18).

Accurate evaluation and quantification of MR severity are crucial to assessing the valve status to decide on required interventions. This led to the introduction of new instruments and modalities. Three-dimensional (3D) techniques have improved the measurements, for instance, on Rvol and the ventricle diameters (21, 22). Also, new methods like multi-slice CT scan and CMR are introduced, which improve the assessments, and are growingly used to substitute the previous echocardiographic suboptimal results or as alternatives (9, 23).

In the current study, the MR severity of 93 patients was determined using conventional semi-quantitative (VCW) and quantitative (RVOl, RF, EROA) measures. Due to technical difficulties in obtaining these quantitative measures, along with the non-feasibility of TEE as a routine option for further investigations (as a result of limited availability, aggressiveness, and dependence on sedation), we made an effort to identify new parameters which are easier to obtain by TTE and do not rely on operators' expertise. This study introduces new hemodynamic burden indices (MVVTI/LVOTVTI; MVAVTI-i; MVAVTI/LVOTDVTI; E velocity-LA area-i) for this purpose and examines their correlation and diagnostic value to express the severity of the MR. These indices show an excellent diagnostic value in recognizing patients with severe MR. While there are uncertainties about the effect of normalization of the conventional measures on BSA on its diagnostic value (8), we used two indices (MVAVTI-i; MVAVTI/LVOTDVTI) which BSA is contained in them.

To our notice, this is the first time that these indices have been used in this manner. Consequently, similar data was not available for further comparison of the results. Similar studies with larger sample sizes should be conducted to further validate these indices and introduce them to the diagnostic criteria.

Conclusion

This study proposed novel TTE-derived indices of MR hemodynamic burden. We showed that these indices were highly correlated with MR severity. In addition, they were deemed to be significantly accurate predictors of severe MR. Finding and validating new easy-obtaining parameters for describing MR severity will help estimate the MR burden easier. Besides, adding such new indices to old measures may improve their predictive value.

Author contribution

FS : conceptualization, investigation, reviewed, and edited the manuscript.

YP : formal analysis, investigation, data curation, methodology, visualization, wrote the original draft, reviewed, and edited the manuscript.

AR : project administration, formal analysis, investigation, data curation, methodology, visualization, wrote the original draft, reviewed, and edited the manuscript.

AK : investigation, data curation, methodology, wrote the original draft, reviewed, and edited the manuscript.

MAH : investigation, data curation, methodology, wrote the original draft, reviewed and edited the manuscript.

ZK : investigation, data curation, reviewed and edited the manuscript.

NS : supervised, validated, reviewed, and edited the manuscript.

All authors read and approved the final manuscript.

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Table 1- Comparison of echocardiographic parameters of hemodynamic burden between MR severity groups.

Variables	Mild MR (n=29)	Moderate MR (n=29)	Severe MR (n=35)	p-value
MVVTI/LVOTVTI	0.66 (0.58-0.76) ++	0.74 (0.62-0.88) §	1.20 (1.07-1.35) ++ §	<0.001*
MVAVTI-i	19.90 (16.15-23.45) ++	18.50 (15.50-21.45) §	32.60 (29.40-37.70) ++ §	<0.001*
MVAVTI/LVOTDVTI	1.00 (0.86-1.10) ++	1.12 (0.96-1.50) §	2.10 (1.90-2.40) ++ §	<0.001*
E velocity-LA area-i	650.00 (564.00-914.50) ++	990.00 (722.00-1367.00) §	1643.00 (1252.00-2203.00) ++ §	<0.001*

All values are reported as median (IQR). Bonferroni correction was carried out for pairwise comparisons.

i, indexed by body surface area; LA, left atrial; MR, mitral regurgitation; MV, mitral valve; MVA, MV annulus; LVOT, left ventricular outflow tract; VTI, velocity time integral.

* there is a significant (p-value <0.001) difference between the groups.

+ there is a significant (p-value <0.001) difference between mild and moderate groups.

++ there is a significant (p-value <0.001) difference between mild and severe groups.

§ there is a significant (p-value <0.001) difference between moderate and severe groups.

Table 2- Correlation between MR severity and echocardiographic parameters of hemodynamic burden.

Variables	Spearman correlation coefficient	p-value
MVVTI/LVOTVTI	0.776	<0.001*
MVAVTI-i	0.672	<0.001*
MVAVTI/LVOTDVTI	0.822	<0.001*
E velocity-LA area-i	0.698	<0.001*

i, indexed by body surface area; LA, left atrial; MR, mitral regurgitation; MV, mitral valve; MVA, MV annulus; LVOT, left ventricular outflow tract; VTI, velocity time integral.

*p-value<0.001

Table 3- Diagnostic accuracy of echocardiographic parameters of hemodynamic burden for severe MR.

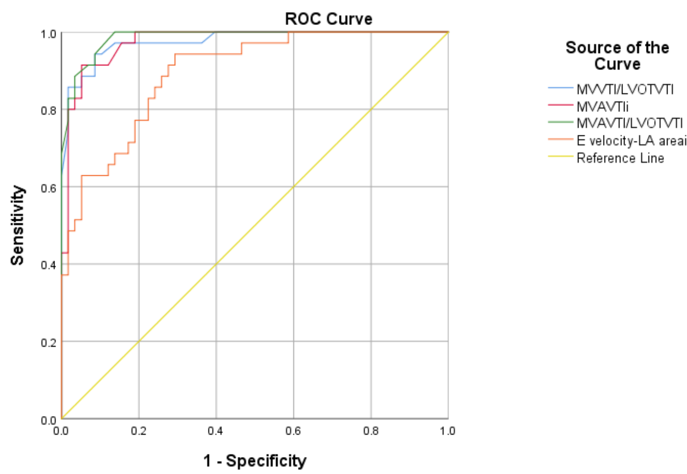
Variables	AUC	95% CI	p-value
MVVTI/LVOTVTI	0.976	0.950-1.000	<0.001*

Variables	AUC	95% CI	p-value
MVAVTI-i	0.975	0.949-1.000	$<0.001^*$
MVAVTI/LVOTDVTI	0.986	0.970-1.000	$<0.001^*$
E velocity-LA area-i	0.895	0.832-0.957	$<0.001^*$

CI, confidence interval; i, indexed by body surface area; LA, left atrial; MR, mitral regurgitation; MV, mitral valve; MVA, MV annulus; LVOT, left ventricular outflow tract; VTI, velocity time integral.

*p-value<0.001

Figure 1- Diagnostic accuracy of echocardiographic parameters of hemodynamic burden for severe MR.



i, indexed by body surface area; LA, left atrial; MR, mitral regurgitation; MV, mitral valve; MVA, MV annulus; LVOT, left ventricular outflow tract; VTI, velocity time integral.