Jurnal
Kardiologi Indonesia
J Kardiol Indones. 2015;36:186-95
ISSN 0126/3773

Clinical Research

Role of Mitral Leaflet Separation Index (MLSI) in Determining Mitral Stenosis Severity

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Objective. To Correlate MLSI with 3-D mitral valve area (MVA) planimetry in determining mitral stenosis (MS) severity.
Background. Mitral Stenosis (MS) is still a major problem in cardiology, and causes of morbidity dan mortality worldwide. Echocardiogrphy plays an important role in assessing mitral stenosis severity. Mitral leaflet separation index (MLSI) is one of simple method that can be used in peripheral by using common ultrasound to assess the severity mitral stenosis.
Methods. We employed a cross sectional study. Mitral stenosis patients who referred for evaluation echocardiography in National Cardiac Center Harapan Kita from April to September 2011. MLSI was obtained by averaging the maximal leaflet separation distance at the tips in diastole in parasternal long-axis and apical four- chamber views. 3-Dimensional (3-D) mitral valve area (MVA) planimetry as a reference. The only exclusion criteria was severe calcification and poor echo window. Echocardiography examination using Philips E33i.
Results. Seventy six consecutive patients were enrolled, 5 subjects were excluded from study because of severe calcification and poor echo window. Proportion of woman is 73.2 % and mostly in age group < 40 years old (43.7 %). Severe mitral stenosis was dominate the subject, 47 subject (66.2 %), moderate was 19 subject (26.8 %), and mild only 5 subjects (7.0 %). Analysis with Spearman correlations obtained a good correlation with $r = 0.70$, $p < 0.001$, good correlation was found in sinus rhythm with $r = 0.78$, $p < 0.001$ and atrial fibrillation with $r = 0.79$, $p < 0.001$. MLSI less than 0.69 cm predicted severe MS with 85 % sensitivity and 82.4 % specificity.
Conclusions. Mitral leaflet separation index (MLSI) has a good correlation with 3-D MVA planimetry. MLSI less than 0.69 cm can estimate severe SM.

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(J Kardiol Indones. 2015;36:186-95)

Keyword: *Mitral Stenosis (MS), Mitral leaflet separation index (MLSI), 3-D mitral valve area (MVA) planimetry.*

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Penelitian Klinis

Peranan Mitral Leaflet Separation Index (MLSI) dalam Menentukan Severitas Stenosis Mitral

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Tujuan. Mendapatkan korelasi antara pemeriksaan MLSI dengan pemeriksaan ekokardiografi 3-D *mitral valve area* (MVA) planimetri dalam menentukan severitas stenosis mitral (SM).
Latar Belakang. Stenosis mitral (SM) masih merupakan masalah utama di bidang kardiologi, dan penyebab morbiditas dan mortalitas di seluruh dunia. Ekokardiografi memegang peranan penting didalam menilai severitas SM. *Mitral leaflet separation index* (MLSI) merupakan salah satu metode sederhana yang dapat digunakan didaerah perifer dengan menggunakan ultrasonografi umum untuk menilai severitas SM.
Metode. Penelitian ini merupakan studi potong lintang. Pasien SM yang menjalani evaluasi ekokardiografi di Pusat Jantung Nasional Harapan Kita dari bulan April sampai September 2011. Pasien SM dinilai severitasnya dengan MLSI dan 3-Dimensi (3-D) *mitral valve area* (MVA) planimetri sebagai rujukannya. Kriteria eksklusi hanya pada pasien dengan kalsifikasi berat dan poor echo window. Penilaian MLSI merupakan nilai rata-rata pada posisi *parasternal long aksis* (PLAX) dan apikal posisi *4-chamber* fase diastolik pada saat pembukaan maksimal ujung katup mitral. Pemeriksaan ekokardiografi menggunakan Philips E33i.
Hasil. Dari 76 pasien SM yang menjalani ekokardiografi 3-D MVA planimetri, 5 subyek dikeluarkan dari penelitian oleh karena kalsifikasi yang berat dan *poor echo window*. Karakteristik subyek dengan proporsi perempuan lebih banyak (73,2 %), dan lebih banyak pada kelompok umur < 40 tahun (43,7 %). Derajat SM berat 47 subyek (66,2 %) mendominasi subyek, SM sedang 19 subyek (26,8 %), SM ringan 5 subyek (7,0 %). Analisa dengan korelasi Spearman didapatkan korelasi yang kuat dengan r = 0,70, p = 0,000, sedangkan pada irama sinus didapatkan r = 0,78, p = 0,000 dan atrial fibrilasi didapatkan r = 0,79, p < 0,001. MLSI kurang dari 0,69 cm memprediksi SM berat dengan sensitifitas 85 % dan spesifisitas 82,4 %.
Kesimpulan. Mitral leaflet seperation index (MLSI) mempunyai korelasi yang baik dengan pengukuran MVA menggunakan 3-D planimetri. MLSI kurang dari 0,69 cm dapat mengestimasi SM berat.

(J Kardiol Indones. 2015;36:186-95)

Kata kunci. *Stenosis mitral (SM), Mitral leaflet separation index (MLSI), 3-D mitral valve area (MVA) planimetri.*

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Introduction

Background

Mitral stenosis (MS) is one of the leading cause of morbidity and mortality in the world, especially in developing countries. MS was first reported by Raymond de Vieussens on 1705.[1] In 2003, Euro Heart Survey stated that 12% of all valvular heart disease was MS.[2] To date, Echocardiographic evaluation holds essential role regarding determination of MS Severity, whereas catheterization methods of measurement are slowly being left behind.[3]

World Health Organization (WHO) estimated that over 15.6 million people had Rheumatic Heart Disease (RHD). The prevalence of RHD in Southeast Asia was 0.8 per 1000 populations.[4,5] In Australia, Carapetis et al found that RHD incidence is declining along as increasing age, but its prevalence remains steadily increase.[6] Sliwa et al. in Africa, found that 72% of all valvular heart defects were caused by RHD, and mitral stenosis (MS) is the most common cardiac pathology of RHD.[7] Along with decline in RHD prevalence, nowadays, MS has never been exclusively found as a single valve defect without other valve involvement.[8] In the period of 2007-2010, at National Cardiac Center Harapan Kita (NCCHK), the amount of MS cases was about 200 cases a year.

Echocardiography holds an essential role in diagnostic and evaluation of valvular heart disease, and currently the most preferable non-invasive method to determine severity of valve stenosis. Marijon et al. showed that RHD prevalence in Cambodia and Mozambique was 10 times higher when using echocardiography as screening method compared to clinical screening only.[9] Reddy et al. also stated that echocardiographic evaluation must be routinely done in order to detect frequently missed features on routine physical examination.[8] Determination of stenosis severity using echocardiography is the basis of clinical decision. Because of that, echocardiography is a standard in determining MS severity.[10]

MS severity determination is very important for diagnostic, therapeutic and prognostic purposes. It is used most importantly in choosing between Percutaneus Transvenous Mitral Commisurotomy (PTMC) or surgical approach in dealing with MS cases. The echocardiographic evaluations routinely done were measurement of Mitral Valve Area (MVA) in 2 dimensional or 3 dimensional using methods such as planimetry, pressure half time (PHT); Mitral valve gradient, and systolic pulmonary artery pressure. These methods are routine use in determining severity of mitral stenosis.[11,12] However, every method has its own superiorities and flaws.

Mitral Leaflet Separation Index (MLSI) is one of the methods that can be done using common 2-D echocardiography examination. The examination uses parasternal long axis and apical 4 chamber view, and measures width between two tips of mitral leaflet during mid-diastole. In 1979, Fisher et al. was one of the first that discover positive correlation between M-mode MLS and catheterization.[13] Seow SC et al. studied 88 MS patients and found significant correlations between MLSI and 2D MVA planimetry ($r=0.91$; $p<0.01$) and PHT ($r=0.86$; $p<0.01$), similar result was also found in MS patients with atrial fibrillation ($r=0.86$ and $r=0.79$; $p<0.01$).[14] Holmin C et al. also find good correlation between MLSI and 2D MVA planimetry in MS patients.[15]

The rationale of using MLSI method is because of the structure of mitral valve that has 3-dimensional shaped so that the measurement of valve cusp separation with 2-dimensional echocardiography may be more accurate.[15] By taking a piece of two fairly orthogonal views, the index can provide substituting images for measuring MVA. Thus, the main advantage of MLSI compared with planimetry lies in its simplicity and ease of making measurements. MLSI is not recommended to replace other tests that have been commonly used in assessing the severity of mitral stenosis, but may be used in addition to these methods.[13]

Recently, Gorlin's equation that is based on catheterization examination is considered as a standar in the measurement of MVA. However, 3-D MVA planimetry has better correlation when compared with the other echocardiography methods, the homogenous data can be retrieved on any planes, it is possible to cut precisely at the tip of mitral valve, so we can measure the anatomy of mitral valve area accurately. The most optimal measurement of mitral valve area is on the two long axis view along mitral valve is almost perpendicular to each other, which is described by the navigation on the line of intersection. Short-axis cross section is positioned furthest from the tip of mitral valve leaflets, which is this area is the place of planimetry measurement.[16] In addition, the assessment of MVA is anatomically useful because it does not depend on the hemodynamic state, unlike the

measurement of MVA by using other methods.[17]

The first study that measured MVA by using 3-D echocardiography was performed by Kupferwasser et al. and Chen et al. in which they compared planimetry 3-D and PHT 2D and the Gorlin's equation.[18,19] The 3-D transthoracic echocardiography examination also showed accurate result to assess mitral valve area. Sugeng et al. and Zamorano et al. proved that TTE 3-D compared with planimetry, PHT, and PISA 2-D show more accurate results when compared to Gorlin's equation to assess mitral valve area.[20,21]

Until now, there are few studies that compare MLSI and other methods of echocardiographic measurement in determine MS severity. Some studies had shown good correlation between MLSI and 2D echo, meanwhile severity evaluation using 3D echo is still not popular. This method can be used for screening purposes in peripheral areas using common ultrasound device.

This research is meant to give input and additional data in determining MS severity. We hope this research can provide a method that is simpler compared to the others, so that it can be used in other centers using common ultrasonogram, and as a valuable screening tools to determine MS severity.

Methods

This is a cross-sectional analytic study. The objective is to find out correlation between 2D MLSI echocardiography and 3D MVA planimetry. This study took place at Cardiology and Vascular Medicine Department of Faculty of Medicine Universitas Indonesia–National Cardiac Center Harapan Kita, in the period of April 2011–September 2011. The population is all patients that have been diagnosed with MS and underwent echocardiography evaluation in the Imaging and Non Invasive Division, and haven't had surgery prior to the time frame. This study used consecutive sampling. Subject variability will not affect the study because all examination was done in the same time. With no time difference, variability will not be significant. By using consecutive sampling, we were trying to get as much sample as possible. The inclusion criteria all MS patients that have echocardiography examination and the exclusion criteria are echocardiograms that are poor echo window and severe mitral leaflet calcification seen on echocardiogram.

Research Procedure, Echocardiography was done using iE 33 Philips. MLSI was taken at parasternal long axis view and apical 4 chamber view on mid diastolic phase at the time of maximal opening of mitral leaflet, measurement was done from leaflet's inner edge to inner edge, mean value from 3 beats (at Sinus rhythm) and 5 beats (at AF rhythm) was taken.[15] 3D MVA planimetry was done with same device, measuring distance between leaflet tips and taken at apical 4-chamber, 3-chamber or 2-chamber view in mid diastolic.[21]

Data Analysis, Normality test was using coefficient of variant and data presented as mean values ± standard deviation or median values for continuous data. Correlation Spearman test was used with abnormal distribution value, ROC curve was used to determine meeting point of MLSI to predict severe mitral stenosis with MVA 1 cm^2. Inter and intra observer analysis was using cronbach alfa and intraclass correlation. All data was analyzed using SPSS 11.5.

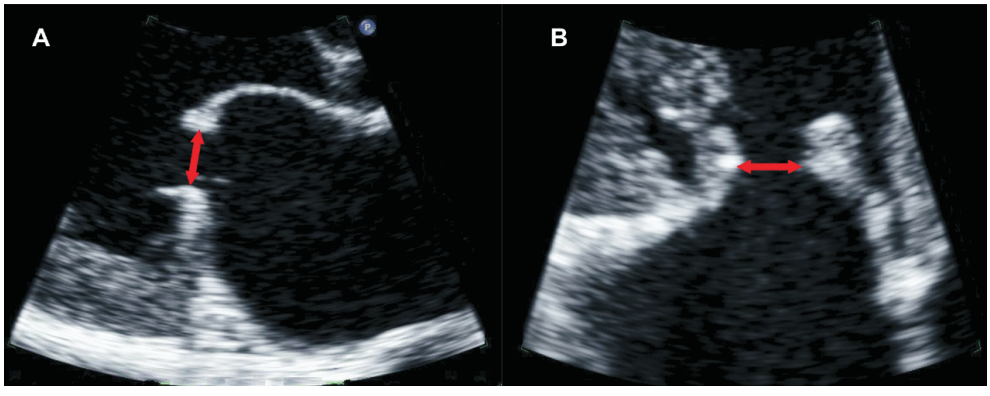


Figure 1. Mitral Leaflet Separation Index (MLSI) measurement, parasternal long axis view and apical 4-chamber view.

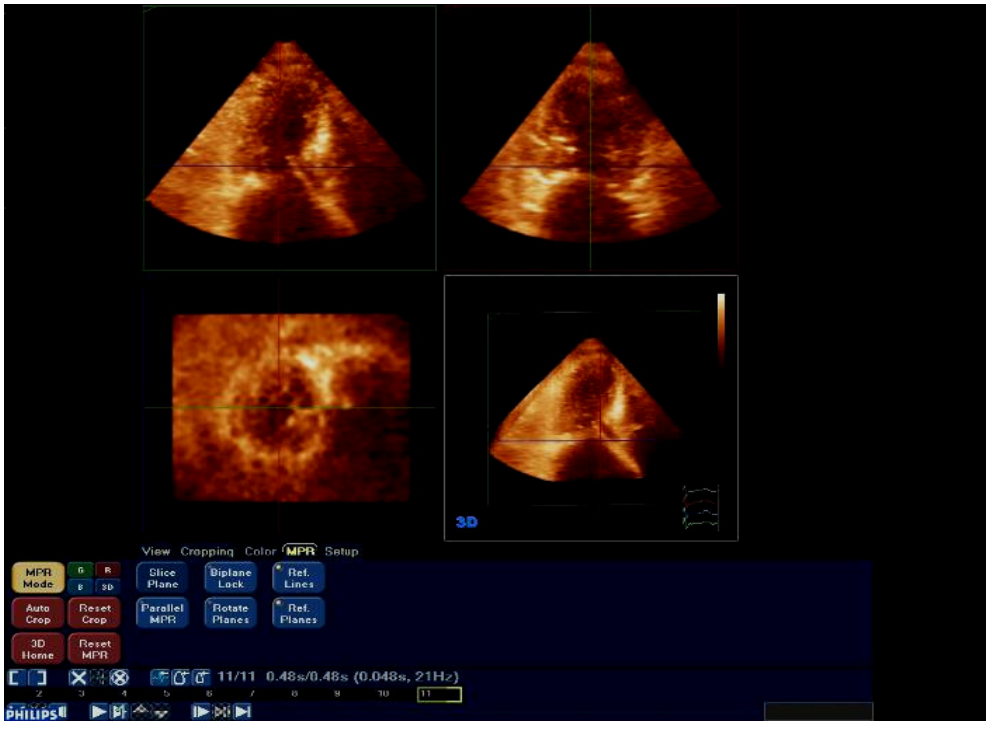


Figure 2. 3-D MVA planimetry measurement 3 orthogonal plane.

3D MVA planimetry is the effective area of mitral leaflets orifice's at mid diastolic phase using 3D echocardiography, values in cm^2 and MLSI is mean value of distance masured between leaflets of mitral valve in mid diastolic phase, values in cm[14,15]. MS Severity (based on MVA)[10] ; Mild : > 1.5 cm^2, Moderate : 1.0 – 1.5 cm^2, Severe : <1.0 cm^2

Table 1. Subject based on demographic characteristic (n=71)

Demographic Characteristic	Amount	%
Sex		
Male	19	26.8
Female	52	73.2
Age Group		
< 40	31	43.7
40 – 49	23	32.4
50 +	17	23.9

Result

Subjects Characteristic

There were 71 MS patients enrolled in this study, out of 76 that qualified inclusion criteria. Five other subjects were excluded because of severe calcification and unreadable echocardiographic images. RHD was the etiology of all 71 MS cases in this study. Female subjects was 73.2% compared to male 26.8%; and more dominant in age groups less than 40 years old. (Table 1.)

Most subjects have severe mitral stenosis (66.2%), mild stenosis only appear 7% cases. Pure MS were only found in 36.6% cases, while the rest have additional problems such as mitral regurgitation, aortic stenosis and regurgitation, and tricuspid regurgitation. Most of MS patient, have severe PH (40.8%), 6 of them (8.5%) had history of prior PTMC. About 69% subjects showed atrial fibrillation on ECG recording and 56.3% had NYHA functional class II. Thrombus formation were only seen in 16.9% patient on transthoracal echo evaluation, meanwhile Spontaneous echo contrast finding was 32.4%. (Table 2.)

Correlation between MLSI and 3D MVA Planimetry

With Spearman correlation test, we can infer that a strong correlation exist between MLSI and 3D MVA

Table 2. Distribution of subjects according on medical risk characteristic (n=71)

Medical Risk	Amount	%
MS Severity		
Mild	5	7.0
Moderate	19	26.8
Severe	47	66.2
Pulmonary hypertension		
Normal	3	4.2
Mild	18	25.4
Moderate	21	29.6
Severe	29	40.8
Other valve abnormality		
None	26	36.6
Any abnormality	45	63.4
Intervention		
None	65	91.5
History PTMC	6	8.5
NYHA Functional class		
I	27	37.0
II	40	56.3
III	4	5.6
IV	0	0
Electrocardiography		
Sinus Rhythm	22	31.0
Atrial Fibrillation	49	69.0
Trombus		
Negative	36	50.7
SEC	23	32.4
Positive	12	16.9

PTMC; Percutaneous Transvenous Mitral Commisurotomy, SEC; Spontaneous Echo Contras

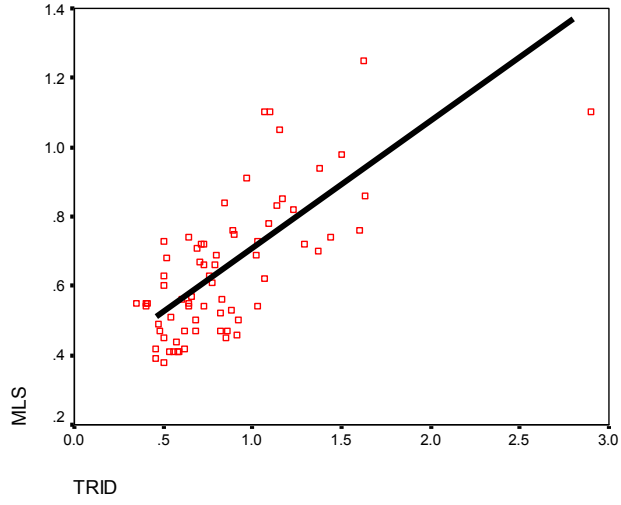
Table 3. Echocardiographic Parameter Result

Variable	Value	95% CI	
		Low	High
LVEDD	44.2±8.2	42.3	46.1
LVESD	30.3±7.4	28.6	32.0
EF	58.7±10.1	56.3	61.0
LA Volume Index	79 (45-328)	80.7	111.1
TAPSE	1.8 (0.6-2.9)	1.6	1.8
LA diameter	50.3±6.5	48.8	51.8
mPAP	30.0 (5-50)	24.0	30.8
MLSI	0.6 (0.38-1.25)	0.6	0.7
3D MVA Planimetry	0.8 (0.35-2.9)	0.8	0.9
TVG	44.0(0-107)	44.0	54.9
Wilkin's Score	6.0(4-11)	6.2	7.0

LVEDD; Left Ventricle End Diastolic Diameter, LVESD; Left Ventricle End Systolic Diameter, EF; Ejection Fraction; LA; Left Atrium, mPAP; mean Pulmonary Artery PressureTVG; Tricuspid Valve Gradient

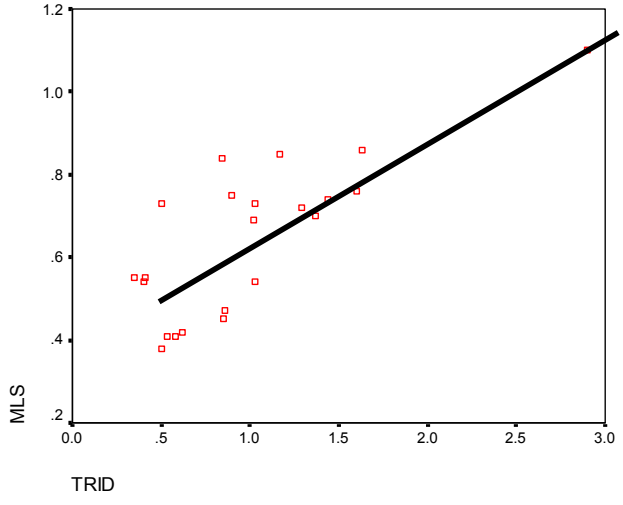
planimetry (r = 0.70 and p <0.001) (figure 3.). Sub group analysis showed consistent result. In sinus rhythm sub group, r = 0.78 & p<0.001 and in AF sub group r = 0.79 and p<0.001 (figure 4. & figure 5.).

Receiver operating characteristics curve showed that severe MS with MVA less than 1 cm2 occur if MLSI was less than 0.69 cm, with 85% sensitivity and 82.4% specificity (figure 6.)



Spearman test, r = 0.70, p < 0.001

Figure 3. correlations between MLSI and 3D MVA planimetry



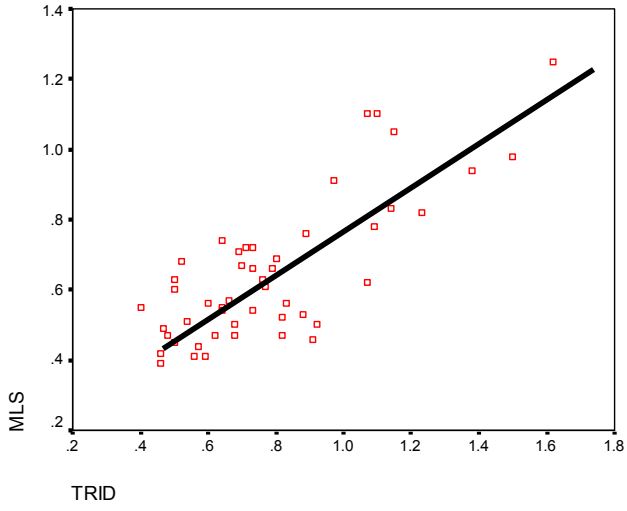
Spearman Test, r = 0.78, p < 0.001

Figure 4. correlations between MLSI and 3D-planimetry on subjects with sinus rhythm.

Table 4. Mean values of MLSI and 3D MVA Planimetry in Sinus rhythm and Atrial Fibrillation subgroup

Variable	SR (n=22)		AF (n=49)		p
	Mean	SD	Mean	SD	
MLSI value	0.645	0.187	0.646	0.203	0.770
3-D value	0.992	0.580	0.786	0.278	0.232

Keterangan: Mann Whitney Rank test (non parametric)



Spearman test, r = 0.79, p < 0.001

Figure 5. correlations between MLSI and 3D-planimetry on subjects with AF.

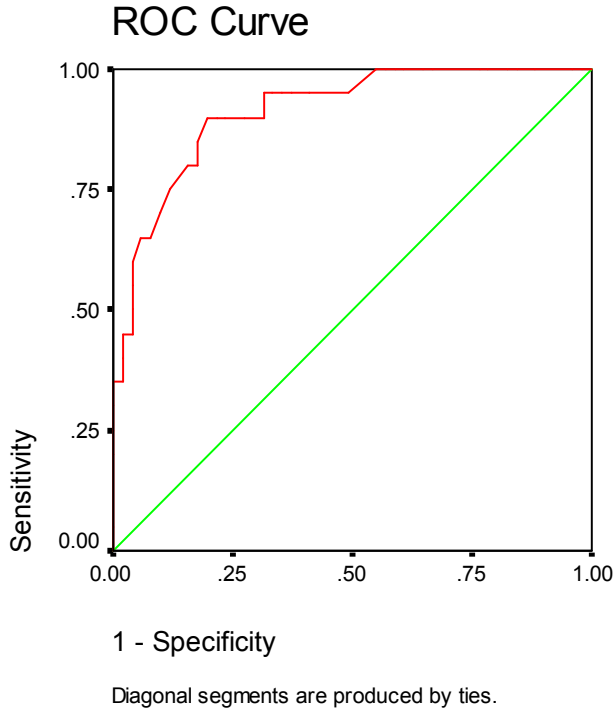


Figure 6. ROC analysis of MLSI values, to identify severe MS with MVA < 1 cm^2

Inter and Intra observer variability on MLSI measurement

In this study, efficacy measurement of MLSI method was verified with the first examiner, and the result was appropriate. This can be seen from cronbach α value and intra class correlation level 0.99; meanwhile inter observer variability showed 0.94 (table 5.)

Table 5. interobserver and intraobserver variability in mitral valve assestment with MLSI

Inter observer		
Variable	Cronbach's α	ICC (95% CI)
MLSI	0.943	0.943 (0.867 - 0.975)
Intra observer		
Variable	Cronbach's α	ICC (95% CI)
MLSI	0.991	0.991 (0.979 - 0.996)

Discussion

At the present time, echocardiography is a gold standard of diagnostic method to determine MS severity.[10,22] The methods that are commonly used to determine MVA are 2D planimetry, PHT, CE, PISA, and 3D planimetry, and some indirect method such as mMVG and SPAP. However, all those methods have their own advantages and disadvantages.[3,10]

Recently, 3-D MVA planimetry is one of the method that is more accurate for non invasive examination approaches Gorlin's equation. Sugeng et al. and Zamorano et al. proved that 3-D MVA planimetry compared with 2-D MVA planimetry. Both

of PHT and PISA showed the more accurate result when compared with Gorlin's equation in order to asses the mitral valve.[20,21] Binder et al. also got that 3-D MVA planimetry can give more accurate image when compared with 2-D MVA planimetry and PHT.[16]

MLSI is such a simple and accurate method for this purpose. Fisher, in 1979 have done the research by using echocardiography M-mode compared with Gorlin's equation for the first time and have found strong correlation.[13] The rationale of MLSI method is due to the 3-dimensional shaped structure of mitral valve so that the measurement of the separation of the valve leaflets by 2-D echocardiography may be accurate.[13]

In this study, there were more women (73.2%) than men (26.8%). Such result also have been found in some studies such as Holmin et al. and Vimal Raj et al. that found the prevalence of women more than men. In the other hand, the data from medical records of National Cardiovascular Center Harapan Kita in 2010 also got that the prevalence of mitral stenosis in women was 63.2%. [15,23] Most cases of mitral stenosis were found in the age group under 40 years old (43.7%).

The cases of severe mitral stenosis were more prevalent (66.2%) than the mild to moderate ones. The cases that were accompanied by pulmonary hypertension were found with severe condition (40.8%), moderate condition (29.6%) and the rest is normal to mild condition.

Most of subjects were also suffered from another valve abnormality, such as mitral regurgitation, aortic regurgitation, aortic stenosis, and tricuspid regurgitation, its prevalence was 63,4%. There were 6 (8.5%) subjects with the history of BMV. Forty nine (69%) of the subjects in this study were found with AF rhythm, and 22 (31%) with sinus rhythm. This finding is quite different with the result from Seow et al. and Vimal Raj et al. that found the AF cases in 36.8% and 26.7%, respectively.[14,23] This is probably because of in this study, the proportion of subjects were suffered from severe mitral stenosis is larger than the mild or moderate cases.

In this research, the prevalence of subjects with NYHA functional class I was 25 (35.2%), NYHA functional class II was 40 (56.3%), and NYHA functional class III and IV was 6 (8,4%). Younan H, in 2010 found that most of the cases were in NYHA functional class III (40%).

In this study was found that subjects with EF 58.7±10.1 ; LVEDD 44.2±8.2 ;and LVESD 30.3±7.4. The MLSI value with the mean 0.6 ± 0.2 (p <0,001 and from 3-D planimetry was found with mean 0.8±0,4 (p < 0.001). There was a strong correlation by Spearman analysis between MLSI and 3-D MVA planimetry with r = 0.7, p<0.001. On the analysis of subgroup with sinus rhythm, there was also strong correlation with r = 0.78, p<0.001. The same result was also found by Seow et al. and Vimal Raj et al. on the subjects with sinus rhythm by using 2-D MVA planimetry examination with r = 0.92, p<0.001 and r = 0.87, p<0.001, respectively.[14,23] In the other hand, in subjects with AF rhythm were also found a significant correlation with r = 0.79 and p<0.001 (Table 6.).

Based on the ROC curve, it was found that MLSI value below than 0.69 cm can be used to predict severe mitral stenosis with sensitivity 85% and specificity 82.4%. The study that was conducted by Seow et al. found that MLSI value below than 0.81 can predict severe mitral stenosis with sensitivity 92.3% and specificity 100%.[14] The other study by Vimal Raj found the result that MLSI value below than 0.8 can predict severe mitral stenosis with sensitivity 92% and specificity 92%.[23]

Table 6. Correlation MLSI with 3-D MVA planimetry

	r	P value
MLSI	0.70	0.000
MLSI with Sinus Rhythm	0.78	0.000
MLSI with Atrial Fibrillation	0.79	0.000

In this study, the MLSI examination is such a simple, accurate, and useful method. This was proven by the intra observer and inter observer variability value that showed the good results (0.99 and 0.94) in determining the severity of mitral stenosis. This method also can be used along with another echocardiography mode, in which MLSI showed a significant correlation when compared with other 3-D MVA planimetry echocardiography examination. The same result was also found in the analysis of subgroup subjects. In the subjects with AF, there was a correlation that is as good as in the subjects with sinus rhythm.

The limitations of this study were the imbalance proportion of the sample, the examination was can't be taken on severe calcification and poor echo window. However, MLSI has major advantages because of its simplicity and ease than other examinations. MLSI is not intended to substitute the other echocardiography

methods, but as an additional method that will strengthen in the determination of severity of mitral stenosis.

Conclusions and Suggestions

MLSI has a good correlation with measurements of MVA using 3-D planimetry**,** MLSI value less than 0.69 cm can estimate severe mitral stenosis with MVA < 1 cm^2 with sensitivity 85% and specificity 82.4%.

We suggest MLSI is expected to become a routine method taken in the echocardiography examination for screening purpose of mitral stenosis patients at peripheral regions, which just have common utrasound equipment.

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