Prognostic Value of Left Atrial Volume Index in End Stage Renal Disease Patients

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Abstract

Introduction: Cardiovascular Disease is the leading cause of death in End Stage Renal Disease patients. Left atrial volume index is an established independent risk predictor for mortality in atherosclerotic heart disease. However, Left atrial volume index has not been extensively studied in hemodialysis population. The aim of this study is to assess the impact of Left atrial volume index on mortality in hemodialysis patients.

Methods: This is a descriptive cross sectional study. From January 1, 2013, through April 30, 2018, we evaluated echocardiographic findings of 91 End stage renal disease patients on maintenance hemodialysis. Patient information was collected and data analysed using SPSS version 22 for windows software package.

Results :The average age of the patients was 62.85±12.4 years. The average duration of dialysis was 29.54 months as shown in Table 1.

The mean Left atrial volume index of our dialysis patients was 38.993 ml/m2. The mean Left atrial volume index of 42.62±10.24 ml/m2 in expired patients as compared to 36.6 ml/m2 in alive patients with a p-value of 0.004 shows that Left atrial volume index of expired patients was significantly higher as compared to alive patients (Table 2).

Area under the curve using Receiver operating characteristic curve was found 66.7% which was statistically significant with p-value 0.007, which suggests that the cutoff value of Left atrial volume index for expired patients can be at least 38.5.

61.5% patients that expired had a Left atrial volume index of more than 38.5 ml/m2, whereas 62.7% patients that were alive had a Left atrial volume index less than 38.5 ml/m2 , the p-value 0.02 suggested a significant association of Left atrial volume index with Mortality. Left atrial volume index gives positive association with mortality, for Left atrial volume index greater than 40, the odds ratio was 3.5.

Mortality didn’t give any significant association with Ejection Fraction, Pulmonary artery systolic pressure and EE ratio.

Conclusion :

Increased Left atrial volume index is associated with higher mortality in End stage renal disease patients on maintenance hemodialysis. Increased Left atrial volume index was the best predictor of mortality among measured echocardiographic parameters in our hemodialysis population.

Background

Patients with End-Stage Renal Disease (ESRD) have an increased risk of premature cardiovascular disease. [1]Diagnosing Cardiovascular disease in patients on hemodialysis is challenging as patients

frequently do not experience symptoms or present with atypical symptoms. Left atrial (LA) size is part of cardiac remodeling in a variety of cardiovascular diseases and a predictor of cardiovascular morbidity and mortality. [2–5] A dilatation occurs in a number of disease processes such as left ventricular hypertrophy and failure, aortic and mitral valve diseases and is a powerful predictor of heart failure, stroke, and mortality. [6–10] Increased LAVi, which is a component of the algorithm for Diastolic dysfunction of LV, was shown to predict mortality after myocardial infarction(MI) [8, 11]The American Society of Echocardiography / European Association of Cardiovascular Imaging, recommended LA volume index (LAVI), the value of LA volume divided by body surface area, to measure LA size. [12]

The most widely applied technique for measuring atrial size is two-dimensional echocardiography (2DE). [12, 13, 14] The method of assessing maximal end-systolic anteroposterior dimension of LA from the parasternal long-axis view in M-mode echocardiography is simple and convenient but its accuracy is rather limited by the anatomical confinement afforded by the spine and sternum and the resulting asymmetrical or pillow-shaped enlargement of the left atrium. [15] For these reasons, multiple linear dimensions or measurement of left atrial volume (LAV) especially when corrected for body surface area i.e. left atrial volume index (LAVi), is a more accurate representation of true LA size. [16]

The ASE(American Society of Echocardiography) in 2005 recommended a value of 28 ml/m^2 as the upper limit for normal LAVi and a value of > 40 ml/m^2 for severe dilatation [12] ,but in 2015 Diastology Guidelines updates from the American Society of Echocardiography and the European Association of Cardiovascular Imaging, the upper normal value of LAVi on 2DE has been increased to 34 ml/m^2. [17]

We have previously studied the normal reference range of LAVi in healthy subjects and the prognostic value of LAVi in Chronic kidney disease(CKD) patients in our population.

In the normal population, in the age group less than 40 years, mean LAVi was 21.7 ml/m^2 (range 10–30 ml/m^2). In more than 40 years of age it was 23.14 ml/m^2 (range 15–28 ml/m^2). [18]

In another study conducted on 170 patients at our center, patients with CKD had a higher median LAVi [30.93 (range 6–69) vs 23 (range 10–35) in patients without CKD]; p-value < 0.001. [19]

The mean LAVi and its correlation with other echocardiographic parameters has not been well studied in our hemodialysis population. The association of LAVi with mortality in hemodialysis(HD) patients is not well known. The aim of this study is to assess the prognostic value of LAVi in hemodialysis patients, compared with previously established clinical and Doppler echocardiographic parameters and to study the impact of increased LAVi on mortality in dialysis patients.

Methods

Patients

From January 1, 2013, through March 31, 2018, we evaluated echocardiographic findings of 90 ESRD patients on maintenance hemodialysis with an average follow-up of 3.7±1.0 years. Patients' demographic and clinical data such as age, gender and comorbid conditions were recorded.

Patients who had the following were excluded :

Underlying malignancy , Decompensated liver cirrhosis , Immunosuppressive therapy, LV EF<25%, Severe Mitral stenosis or Mitral Regurgitation, patients on peritoneal dialysis or kidney transplantation before the initiation of hemodialysis, Acute Kidney Injury, less than 3 months on hemodialysis.

Echocardiography

LA Measurements:

The study patients underwent TransThoracic Echocardiography,(TTE) using Toshiba, Aplio 300 system, Model TUS-A300. All patients were examined in the Left lateral position.TTE is the recommended approach for assessing LA size and it was used in our study. (TEE, is not used because the entire left atrium frequently cannot fit in the image sector). LA size is measured at the end of LV systole, when the LA chamber is at its greatest dimension. Care is taken to avoid foreshortening of the left atrium. Acquisition of the left atrium from the apical approach is done. Care is taken to have the base of the left atrium at its largest size, so that the imaging plane passes through the maximal short-axis area. LA length is also maximized to ensure alignment along the true long axis of the left atrium. The lengths of the long axes measured in the two-and four-chamber views were almost similar. When tracing the borders of the left atrium, the confluences of the pulmonary veins and the LA appendage were excluded. The atrioventricular interface was represented by the mitral annulus plane and not by the tip of the mitral leaflets. LA volume is measured using the disk summation method. [20, 21] The LA endocardial borders were traced in both the apical four and two chamber views. Gender differences in LA size were accounted for by indexing to BSA. [22-30]

Left atrial volume was taken as the volume of blood in left atrium at the end of the systole, just prior to the opening of Mitral valve. Standardized planimetry was used to trace the borders of left atrium and left ventricle. Left atrial volume index (LAVi) was computed by dividing the left atrial volume by the body surface area of the individuals, as shown by formula

LAVI= LAV(ml)/BSA(m^2).

Other parameters computed from the echocardiography were LV Ejection Fraction ,mitral regurgitation, left ventricular hypertrophy, E/e´ ratio and pulmonary artery systolic pressure (PASP).

Statistical Analysis :

Data was analysed using IBM SPSS. Data was expressed as mean ± Standard Deviation(SD), and percentages for different parameters. Quantitative variables were expressed as mean ± SD, while Qualitative variables were expressed with numbers and percentages. Effect of LAVI on Mortality was evaluated by binary Logistic Regression. ROC Curve was used to determine the cutoff value of LAVI for expired patients. Association between LAVi and mortality was assessed by Pearson Chi Square test. P value less than 0.05 was considered as significant. Relationship between LAVi and other echocardiographic parameters was assessed using scatter plots. Sampling technique was non probability purposive sampling.

Results

The average age of the patients was 62.68 ±12.47 years. 51/90 were males (56.7%) and 39/90(43.3%) were females. Average body surface area was 1.77 m^2 and mean height was 65.09 inches. The average duration of dialysis was 29.54 months as shown in Table 1.

Table 1

Patient Demographics

Age(years)	62.68 ± 12.474
Gender	51 (56.6%)males 39(43.3%) females
BSA(m^2)	1.7718 ± 0.2446
Height(inches)	65.09± 3.802
Duration on dialysis(months)	29.54 ± 28.98
Diabetes Mellitus	74/90
Hypertension	86/90
Dyslipidemia	28/90
Smoking	27/90
PCI	9/90
CABG	11/90

Among the comorbidities, hypertension was the most prevalent with 86(95.5%) patients being hypertensive. This was followed by diabetes in 74 patients(82.2%) and dyslipidemias in 28 patients(31.1%). 27/90(30%) patients had a history of smoking. 9 patients had Percutaneous Coronary Intervention(PCI) and 11 had coronary artery bypass grafting(CABG).

The mean LAVi of our ESRD patients was 38.99 ml/m^2 with minimum value of 12 ml/m^2 and highest value of 72ml/m^2 and standard deviation of ± 10.57 as shown in Table 2.

Table 2 Echocardiographic Findings of patients					
	EF(%)	PASP (mm Hg)	LAVI(ml/m^2)	PCWP (mm Hg)	E/e´
Mean	**53.69**	**43.62**	**38.993**	**17.34**	**12.90**
StandaradDeviation	**13.109**	**14.779**	**10.5705**	**3.544**	**3.464**

The mean LAVI of 42.62±10.24 ml/m^2 in expired patients with p-value 0.004 suggested mean LAVI of Expired patients was significantly higher as compared to alive patients (Table 3).

Table 3

Comparison of Mean LAVI among Alive and Expired Patients

Mortality	N	Mean LAVI (ml/m^2)	Standard Deviation	p-value
All Patients	90	38.993	10.57	-
Alive	51	36.22	10.04	0.004*
Expire	39	42.62	10.24	
*p<0.05 was considered significant using independent sample t-test				

Results of logistic regression showed that expired patients were 1.067 times more likely to be found with higher LAVI as compared to alive patients(95% confidence interval for odds ratio was (1.018- 1.119) with significant p-value 0.007) as shown in Table 4.

Table 4

Effect of LAVI on Mortality using Binary Logistic Regression

parameters	B	S.E.	Wald	df	p-value	Odds ratio	95% C.I.for odds ratio	
							Lower	Upper
LAVI	0.065	.024	7.260	1	0.007	1.067	1.018	1.119
Constant	-2.822	.977	8.342	1	0.004	0.060		
*p<0.05 was considered significant for odds ratio								

Logistic regression results suggested, Area under the curve using Receiver operating characteristic curve (ROC curve) was found 66.7% statistically significant with p-value 0.007, the ROC suggested the cutoff

value of LAVI for expired patients can be at least 38.5(Figure 1)

Table 5

Association of LAVI with Mortality using Pearson Chi Square test

LAVI		Mortality		Total
		Alive	Expire	
LAVI <=38.5	n	32	15	47
	%	62.7%	38.5%	52.2%
LAVI >38.5	n	19	24	43
	%	37.3%	61.5%	47.8%
Total	Count	n	39	90
	% within Mort	%	100.0%	100.0%
*p-value 0.02 obtained using Pearson Chi Square test				

61.5% patients were expired and found with LAVI more than 38.5 ml/m^2, whereas 62.7% patients were alive with LAVI less than 38.5 ml/m^2, the p-value 0.02 suggested a significant association of LAVI with Mortality.

The analysis done above showing LAVI 38.5 as best cut off also giving significant association with mortality obtained using Pearson Chi Square test. LAVi gives positive association with mortality , for LAVI greater than 40, the odds ratio was 3.5.

A significant negative relationship observed between LAVI and EF, r-square showing 4.4% variation in EF was explained by the help of LAVI as shown in Figure 2.

A significant positive relationship observed between LAVI and PASP as shown in Figure 3, r-square showing 20.4% variation in PASP was explained by the help of LAVI.

A significant positive relationship observed between LAVI and E/e´ ratio as shown in Figure 4, r-square showing 21.3% variation in E/e´ ratio was explained by the help of LAVI.

Table 6

Correlation of LAVi with mortality and other echocardiographic parameters

Correlations						
		LAVI	EF%	PASP	EE RATIO	Mortality
LAVI	r-value	1				
	p-value					
EF%	r-value	-.209*	1			
	p-value	.048				
PASP	r-value	.451**	-.243*	1		
	p-value	.000	.032			
EE RATIO	r-value	.461**	-.289*	.330**	1	
	p-value	.000	.012	.007		
Mortality	r-value	.302**	-.176	.172	.163	1
	p-value	.004	.095	.132	.163	
*p-value <0.05 was considered significant for correlation.						

Pearson Correlation analysis showed, LAVI gives 20.9% significant negative relationship with EF, 45.2% significant positive relationship with PASP, 46.1% significant positive relationship with EE ratio, and 30.2% significant positive relationship with Mortality(Table 5).

Mortality didn't give any significant association with EF, PASP and EE ratio as shown in table 6.

Discussion

The mean LAVi in our study population is higher than in the healthy population as well as in CKD population. The mean LAVI in our dialysis patients was 38.93+/- 10.57 ML/M2 as compared to 21.96 +/- 4.189ML/M2 in the normal population and as compared to 33.33 +/- 11.71 ML/M2in the CKD population. [18–19]

In previous studies, LAVi has been shown to be significantly higher in dialysis patients than in healthy subjects. In a study done by Seung Jun Kim et al increased left atrium volume index (LAVI > 32 mL/m 2) was observed in 99 (45.8%) of the CAPD patients [31].

Our study showed that LAVi is an independent predictor of mortality in Hemodialysis patients and as LAVi increases mortality increases. Among all echocardiographic parameters, LAVi is the strongest predictor of Mortality in our ESRD patients. Similar findings were seen in a study by Mayo Clinic of a large cohort of more than 10,000 patients which showed that with every milliliter per square meter increase in LAVi, all-cause mortality risk increased by 3% (hazard ratio [HR], 1.03; 95% CI, 1.02–1.04; P < .001) [32].

Abhayaratna et al in their study showed that LAVi of 34 mL/m2 or greater was an independent predictor of death, heart failure, atrial fibrillation, and ischemic stroke.

Currently most of the focus is on LA volume, which is also a component of the algorithm for Diastolic dysfunction of LV,, in addition to LVH and LV systolic and diastolic dysfunction as an indicator of CV outcomes. It is reported that LA size is a more stable indicator to reflect the severity and chronicity of diastolic dysfunction than any other echocardiographic parameter although it is largely determined by the same factors that influence diastolic LV filling. [33] The E/e' ratio accurately reflects the filling pressures at the time of the examination. In contrast, the LAV is a reflection of the long-term exposure to LV filling pressures. It reflects the beat-to-beat interaction of LV filling pressure and ventricular compliance, making them sensitive to rapid alterations in ventricular preload and afterload

In line with these findings, we demonstrated that increased LAVI was an independent risk factor for mortality, suggesting that LAVI is a more reliable predictor of mortality in patients on hemodialysis as compared to E/e' and EF which are dependent on multiple factors including loading conditions and volume status.

Using the ROC curve and Pearson chi square test we found out that the best cut off value for LAVi that gives significant association with mortality is greater than 38.5 ml/m2 in our dialysis population. LAVi had a significant positive association with mortality. The American Society of Echocardiography criterion for moderate LA dilatation is LAVI > 40 ml/m2, at which the odds ratio was 3.5 in our study.

Only a few studies have evaluated the relationship of LAVi with mortality in ESRD patients. LAVi has shown to be an independent predictor of CV morbidity and mortality in the general population and, more specifically, in ESRD patients on chronic dialysis [30,, 34, 35, 36]The study conducted by Seung Jun Kim et al in 216 patients with CAPD showed that increased LAVI was an independent predictor of all-cause mortality [hazard ratio (HR) 1.05, P = 0.03] and cardiovascular mortality (HR 1.08, P = 0.006). [30]

The E/e' ratio accurately reflects the filling pressures at the time of the examination. It reflects the beat-to-beat interaction of LV filling pressure and ventricular compliance, making them sensitive to rapid alterations in ventricular preload and afterload. In contrast, the LAV is a reflection of the long-term exposure to LV filling pressures. In a Mayo Clinic Study, Left atrial enlargement was independently associated with an increased risk of all-cause mortality in a large cohort of 10,719 patients with normal Left ventricular filling pressure and preserved LVEF. [37]

In the present study, we can surmise that patients with enlarged LA were volume expanded, which might explain the higher mortality rate in these patients. Therefore, more attention should be paid to better control of fluid overload in patients with enlarged LA.

Limitations

This study has been done in our population in Pakistan and the relationship of LAVi with mortality may not be generalised to the general population.

Echocardiographic examinations were performed only at one point in time, it was difficult to determine the consequence of the changes of echocardiographic parameters on patients' clinical outcome. Serial follow-up echocardiography examinations may be of help in understanding the natural history of LA remodeling in HD patients [38]

Number of patients was not large. A larger sample size would further help to improve the significance of the statistical analysis.

Conclusion

Increased LAVi is associated with higher mortality in ESRD patients on maintenance hemodialysis. Increased LAVi was the best predictor of mortality among measured echocardiographic parameters in our hemodialysis population.

Abbreviations

ESRD -End Stage Renal Disease

LA- Left atrium

LAVI-Left Atrial Volume Index

MI-Myocardial Infarction

2DE-2D Echocardiography

ASE-American Society of Echocardiography

CKD-Chronic Kidney Disease

EF-Ejection Fraction

TTE-Trans Thoracic Echocardiography

LV-Left Ventricle

BSA-Body Surface Area

PASP-Pulmonary Artery Systolic Pressure

SD-Standard Deviation

ROC-Receiver Operating Curve

Declarations

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Disclosure of any Conflict of interest:

Conflict of interest: none declared.

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Figures

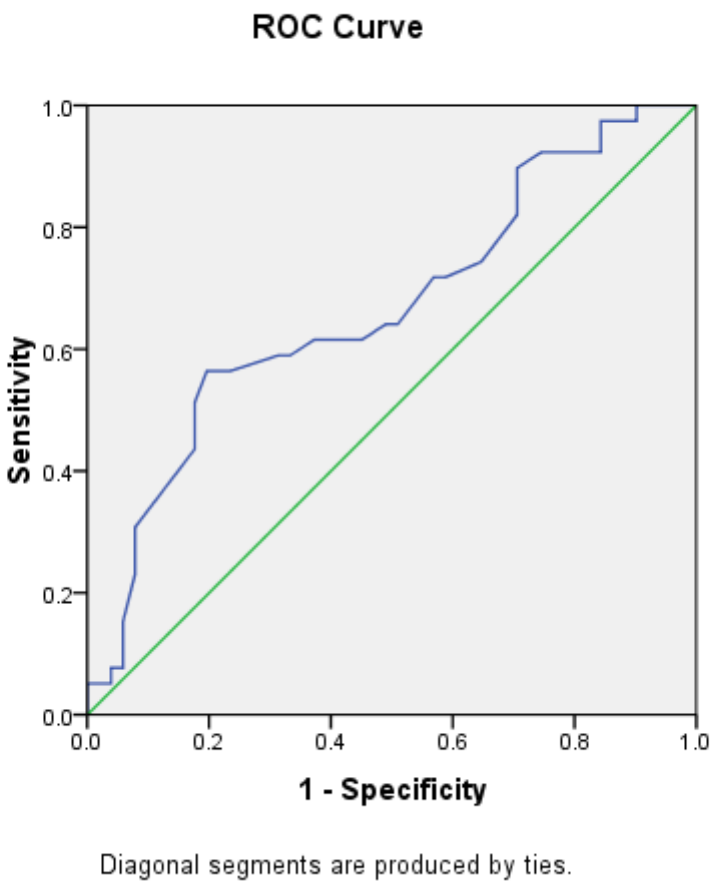

Figure 1

Cut off value of LAVi using ROC Curve

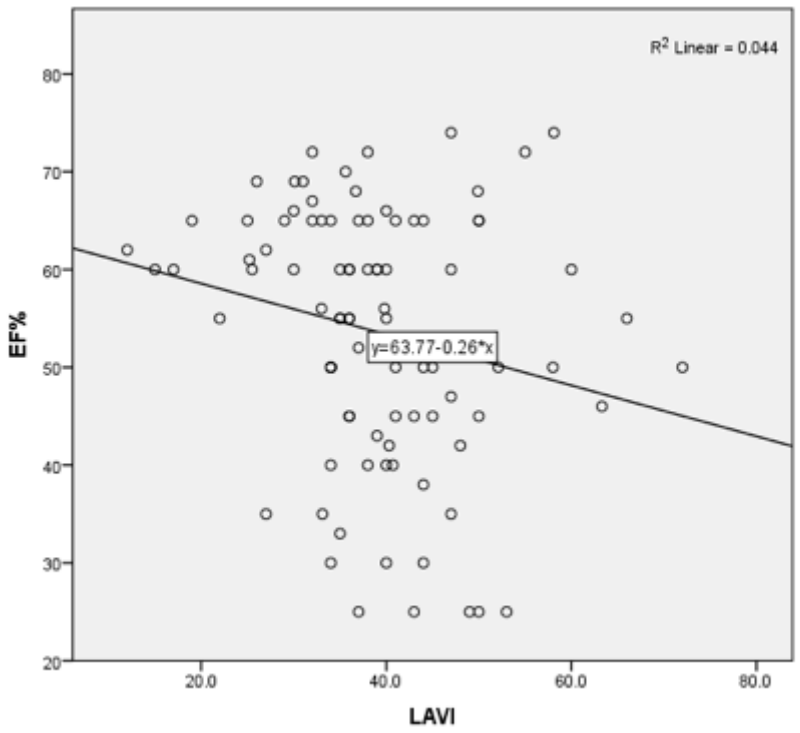

Figure 2

Relationship between LAVi and EF

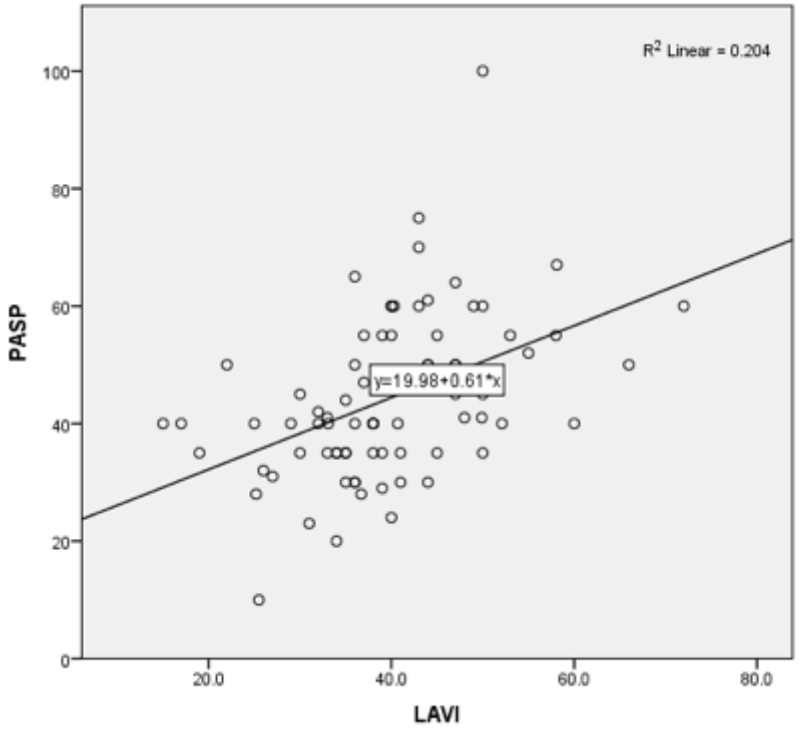

Figure 3

Relationship between PASP and LAVi

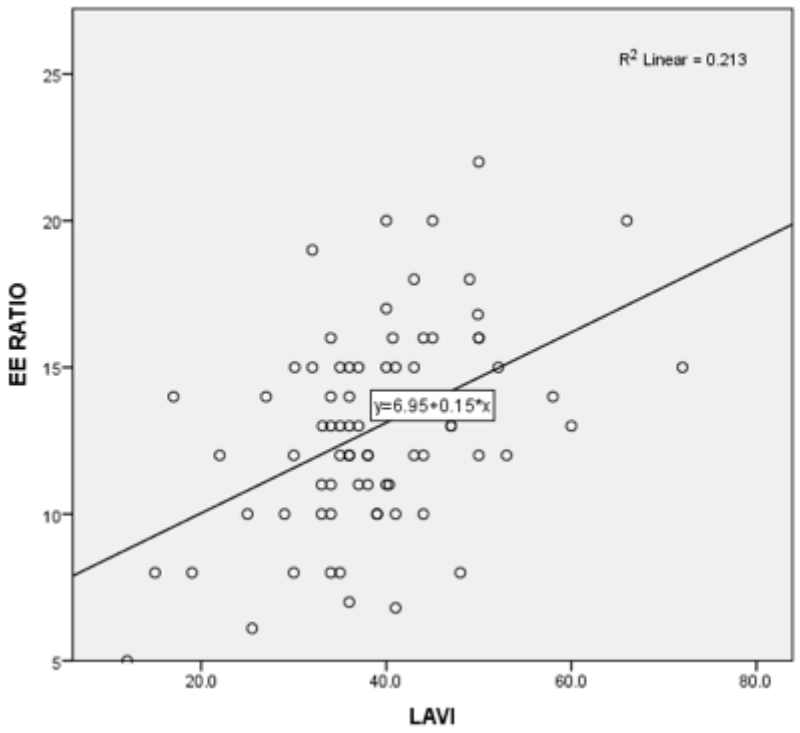

Figure 4

Relationship between LAVi and E'e Ratio