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Study of Prognostic Significance of Global Longitudinal Strain and E/e' Verses Ejection Fraction of Left Ventricle by Echocardiography in Predicting Morbidity and all-Cause Mortality in Kidney Disease Patients

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Abstract: ***Background:*** This study was conducted to evaluate the prognostic significance of global longitudinal strain and e/e' versus ejection fraction of the left ventricle by echocardiography in predicting morbidity and all-cause mortality in kidney disease patients. ***Methods:*** This was a hospital-based study conducted among 56 consecutive patients suffering from renal disease in the Department of Cardiology and Nephrology at DYP Hospital, over a period of 12 months, from September 2022 to August 2023, after obtaining clearance from the institutional ethics committee and written informed consent from the study participants. ***Results:*** In patient death analysis for LVEF and in patient death analysis for GLS, the difference was statistically significant. All cases that died had an abnormal E/e ratio, which is greater than those that survived and is statistically significant. There were 28 patients with LVEF < 50%, and their mean LVEF was 35.14%, out of which 8 patients died during the study period. There was a 12% reduction in LVEF at the end of the one-year study; this reading was statistically significant. There were 28 patients with LVEF >50%, and their mean LVEF was 56.42%. During the study, 2 patients died and survived, and 26 patients had a mean LVEF of 52.05%. There was a 7% reduction in LVEF at the end of the study; as compared to LVEF <50%, there is minimal change in the reduction of LVEF; the findings are statistically significant. There were 45 patients with abnormal GLS whose mean GLS was -10.5%, out of which 10 patients died during the study; the follow-up mean GLS reading of the survived patient was -9.75%; it has deteriorated by 7%; this finding is statistically significant; and those who have normal GLS had a mean of -16.11% and a follow-up mean of 15.71%; there was a 7% deterrence of GLS in one year of study; the findings were statistically significant. ***Conclusion:*** Abnormal GLS is a good prognostic marker of morbidity and mortality in chronic kidney disease patients. The study indicates that global longitudinal strain is a superior guide to estimating LV function than LVEF for detecting myocardial dysfunction in CKD. Larger-scale CKD population studies are needed to verify if GLS offers patients an additional prognostic value when compared to LVEF.

Keywords: Prognostic, Global Longitudinal Strain, E/e' Verses Ejection Fraction, Echocardiography, Predicting Morbidity

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INTRODUCTION

The ratio of the maximum change in myocardial longitudinal length in systole to the initial length is known as the left ventricular global peak systolic longitudinal strain (GLS), which is determined using two-dimensional STE with strain analysis. During systole, the longitudinally shortened LV myocardium is indicated by a negative number in GLS. The LV function performs better the more negatively the GLS value is. The majority of the studies' main conclusions indicated that GLS≥ − 15% was a significant and independent predictor of all-cause death; however, several research recommended different GLS cutoff levels. Even in HF patients with maintained LVEF and CKD patients, GLS is a more objective and sensitive tool for evaluating cardiac functions than LVEF.[1-4] GLS has clear benefits over other markers in that it may detect early structural and morphologic myocardial damage and reveal subclinical LV dysfunction. Not only

is GLS more accessible, readily quantifiable, repeatable, and sensitive, but its accuracy has been linked to magnetic resonance imaging.[3,4]

Subclinical LV systolic dysfunction, as detected by GLS, has been linked in prior publications to unfavourable outcomes in patients with CKD and even ESRD.[5,6,7] Finding the high-risk individuals among CKD patients may let doctors start secondary preventive measures that might reduce morbidity and death, such as better chronic heart failure treatment. A particular focus is on alternative 2D-ECHO approaches. Specifically, patients receiving peritoneal dialysis and predialysis who had intact LVEF (> 50%) had lower GLS (15%), which was linked to a higher likelihood of hospitalisation for heart failure and a higher death rate.[8] Therefore, in certain situations, such as those in which the LVEF is intact, such as in patients who have had volume overload, pressure overload, or both, GLS may be a more appropriate method for evaluating subclinical changes in LVSD. [8,9]

Furthermore, research has indicated that the variables (race, stage of ESRD, risk factors, and comorbidities) that are used to define a maintained LVEF and a decreased GLS are related to variations in the characteristics of the population under study. GLS is a valuable echocardiographic technique that may be used in ESRD patients to identify individuals who have a high-risk prognosis for developing HF or other CEs, despite this variability. In the current study, LVSF using 2D-ECHO, EF (by Simpson's technique), and GLS (by Speckle tracking) were compared via echocardiography to determine the predictive relevance of GLS vs. EF of the left ventricle in patients with renal illness.

AIMS AND OBJECTIVES

- Assessment or study of left ventricular function by echocardiography, the Simpson disc method, speckle tracking (global longitudinal strain), and e/e' with tissue Doppler imaging. In renal disease patients, those are on dialysis.
- Comparative relation of LVEF and GLS [for study parameters: LVEF more than 50% and less than 50%, GLS less than -15 is normal, and more than -15 is abnormal].
- To study the association between left ventricular global longitudinal strain, LVEF, and E/e' to creatinine values
- Comparison of the above echocardiographic parameters in symptomatic patients [i.e., those with h/o hospitalisation] and asymptomatic patients [i.e., those with no h/o hospitalisation].
- Outcome of one-year Follow-up study of LVEF, GLS, and E/e' in all survived patients.
- Correlation of LVEF, GLS, and E/e' values to predict overall morbidity and mortality [hospitalisation and death].
- Inter-correlation of patients with normal LVEF and reduced LVEF to GLS and E/e' parameters
- To study the association of echocardiographic [LVEF, GLS.E/e'] parameters with those who survived and those who are dead.
- To investigate the superior predictors of mortality and all-cause cardiovascular morbidity when compared to global longitudinal strain and ejection fraction.

MATERIAL AND METHODS:

This was a hospital-based study conducted among 56 consecutive patients suffering from renal disease in the Department of Cardiology and Nephrology at DYP Hospital, over a period of 12 months, from September 2022 to August 2023, after obtaining clearance from the institutional ethics committee and written informed consent from the study participants.

Inclusion Criteria

1. Age above 18 years of age
2. All patients with impaired renal function, OPD, or IPD
3. With or without a comorbid condition
4. with primary renal disease or secondary to any other etiological cause

Exclusion Criteria

1. Patients below the age of 18
2. Patients not giving consent or not willing for an initial and follow-up echocardiography examination.

Statistical Methods

The qualitative data was presented using frequency and percentage, and quantitative data was presented using descriptive statistics such as mean, SD, and SEM. for proportion and the chi-square test for association. The level of significance was set at 5%. All p-values less than 0.05 were treated as significant. All calculations were done using SPSS version 19.

RESULTS:

Baseline EF	**GLS**	
	Normal n (%)	**Abnormal** n (%)
Less than 50%	0	28 (62.2)
More than 50%	11 (100)	17 (37.8)
Total	11 (100)	45 (100)
Baseline Parameters – EF and GLS		
χ^2 value = 9.164 df = 1 p value, sig = 0.002		
GLS	**H/O Hospitalization**	
	NO n (%)	YES n (%)
Abnormal	20 (65.6)	26 (96.3)
Normal	9 (34.5)	1 (3.7)
Total	29 (100)	27 (100)
Analysis of Hospitalised Patients during Study with GLS Values		
X value = 8.392 df = 1 p-value, sig = 0.004, Sig		
Table 1		

Total number of patients studied were 56 out of which 28(50%) are having LVEF <50% and another 28 (50%) are having LVEF >50%. Studied 45 (80.35%) patients are having abnormal GLS, and 11 (19.65%) cases are having normal GLS. This difference was statistically significant. Those who had H/O hospitalisation during the study for various illnesses. About 3.7% of the cases had normal GLS, and 96.3% of the cases had abnormal GLS. This difference was statistically significant.

Cases	**Baseline**	**Mean E/e'**	**H/O Hospitalisation**	**Asymptomatic during Study IVO Heart Failure**
LVEF <50%	28	12.5	19(67.85 %)	9(32.15%)
LVEF>50%	28	10.5	8(28.57 %)	20(71.43%)
Normal GLS	11	11.7	1(9.1%)	10(90.9%)
Abnormal GLS	45	8.8	26(57.8%)	19(42.2%)
H/O Hospitalised Patients and No H/O of Hospitalised Patients				
Baseline EF	**E/e** **Abnormal** N (%)		**GLS**	**E/e** **Abnormal** **N (%)**
More than 50%	28 (50%)			
Baseline EF	E/e		Abnormal	45 (80.4)
	Abnormal n (%)		Normal	11 (19.64)
Less than 50%	28 (50%)		Total	56 (100)
Baseline E/e' Mean Values				
Table 2				

There were 90.9% of patients with normal GLS, and 43% of patients had asymptomatic IVO of HF despite having abnormal E/e' values. This finding is statistically significant. All studied patients for LVEF have abnormal E/e' values; this difference was statistically significant. About 70.6% of the cases on dialysis with abnormal GLS and 29.4% with normal GLS had abnormal E/e.

LVEF	**Death**	
	No n (%)	**Yes** n (%)
Less than 50%	20 (43.47)	8 (80.0)
More than 50%	26 (56.53)	2 (20.0)
Total	46 (100)	10 (100)
Patient Death Analysis for LVEF		
χ^2 value = 0.329 df = 1 p-value, sig = 0.566, NS		

GLS	**Death**	
	No N (%)	**Yes** N (%)
Abnormal	35 (76.1%)	10 (100%)
Normal	11 (23.9%)	0
Total	46 (100%)	10 (100%)
Patient Death Analysis for GLS		
χ^2 value = 2.976 df = 1 p-value, sig = 0.085, NS		
Table 3		

About 80.0% of the cases died with an ejection fraction of less than 50.0%, and 20% of the cases died with LVEF greater than 50%. This finding was statistically significant. All the cases that died had abnormal GLS, and this difference was statistically significant.

E/e			**Death**	
			No N (%)	**Yes** N (%)
Abnormal			46 (100%)	10 (100%)
E/e' Mean Values				
Cases	**Baseline**	**Mean E/e'**	**H/O Hospitalisation**	**Asymtomatic during Study IVO Heart Failure**
LVEF <50%	28	12.5	19(67.85 %)	9(32.15%)
LVEF>50%	28	10.5	8(28.57 %)	20(71.43%)
Normal GLS	11	11.7	1(9.1%)	10(90.9%)
Abnormal GLS	45	8.8	26(57.8%)	19(42.2%)
Table 4				

All cases that died had an abnormal E/e ratio, which is greater than those that survived and is statistically significant. There were 28 patients with LVEF < 50%, and their mean LVEF was 35.14%, out of which 8 patients died during the study period. I survived 20 patients, and my mean LVEF was 31.08%. There was a 12% reduction in LVEF at the end of the one-year study; this reading was statistically significant. There were 28 patients with LVEF >50%, and their mean LVEF was 56.42%. During the study, 2 patients died and survived, and 26 patients had a mean LVEF of 52.05%. There was a 7% reduction in LVEF at the end of the study; as compared to LVEF <50%, there is minimal change in the reduction of LVEF; the findings are statistically significant. There were 45 patients with abnormal GLS whose mean GLS was -10.5%, out of which 10 patients died during the study; the follow-up mean GLS reading of the survived patient was -9.75%; it has deteriorated by 7%; this finding is statistically significant; and those who have normal GLS had a mean of -16.11% and a follow-up mean of 15.71%; there was a 7% deterrence of GLS in one year of study; the findings were statistically significant.

E/e Prime

The baseline mean E/e' of all studied patients was 11.35; follow-up of all patients noted a mean E/e' of 13.2. There was a 14.4% rise in the E/e' prime value, which suggests progressive deterioration in left ventricular function. There were 71.43% of patients with normal LVEF and 90.9% of patients with normal GLS who were asymptomatic during the study, in spite of raised E/e', and it further deterred by 14.5%. This required close follow-up until they became symptomatic.

DISCUSSION:

The current investigation showed that deteriorating GLS is linked to poor clinical outcomes and is independently related to a greater all-cause mortality in CKD patients. When it came to predicting death, GLS outperformed other known risk variables for mortality. Additionally, among patients with decreased renal function, our study found a correlation between unfavourable mortality outcomes and impaired GLS (>-16%). Myocardial strain assessment's predictive significance in chronic kidney disease has not been thoroughly studied. GLS was revealed to be a sensitive discriminator over important clinical risk variables in predicting all-cause mortality by Krishnaswamy et al. when they examined the connection between GLS and renal impairment and all-cause mortality.48 Liu et al. found that in a group of 88 stable hemodialysis patients with sustained EF and a mean follow-up of 25.6 ± 9.9 months, impaired GLS was independently linked with all-cause death..[10]

One metric that may be used to assess the LV filling pressure is the E/e′ ratio. It is used to identify diastolic heart failure.[11-13] In individuals with hypertension, the E/e′ ratio is a prognostic factor for the development of CVDs and a measure that properly represents LV filling pressure.[14] The E/e′ ratio in myocardial infarction patients is thought to be a very reliable indicator of survival. Over half of individuals with renal failure had 54 HF.[15] Therefore, it is more crucial to identify HF early and start treating it in individuals with CKD and ESRD. The left arterial pressure and LV relaxation together determine the mitral valve's state, which is reflected in the E value and the value of e′ can be used to gauge how well the myocardium is relaxing. Not only does the size of e′ decrease in aberrant myocardial relaxation, but the mitral valve opens later in the process.[16,17] A ratio of less than eight is regarded as normal, whereas a ratio greater than fifteen indicates that the left ventricle filling pressure has increased.[18-20]

Tissue Doppler echocardiography has been used to assess LV stiffness and filling pressure in patients with normal EF. The current study's findings demonstrate that all LVEF patients had aberrant E/e' values. About 80.0% of the cases died with an E/e of less than 50.0%, and 20% of the cases died with an LVEF of more than 50%. E/e's prime value suggests progressive deterioration in left ventricular function. Patients with an elevated E/e′ ratio had statistically significant death rates. Furthermore, it was shown that the E/e′ ratio was correlated with mortality in individuals with CKD. Deterioration of diastolic function may be a related phenomenon, independent of the stage of CKD. Several variables contribute to the high prevalence of hypertension in patients with CKD. Therefore, echocardiography screening is necessary regardless of the degree of renal function decline. Since there was no statistically significant correlation found between the E/e′ ratio and the degree of renal failure, individuals with CKD should have echocardiography done in order to determine whether there is a link with diastolic failure. Echocardiography examination of the E/e′ ratio is essential for individuals with substantial risk factors (diabetes, hypertension) for the induction of CKD.[21,22] The use of the E/e′ ratio would hasten the early detection of these people, the early diagnosis of diastolic heart failure, the early start of treatment, the amelioration of renal failure, and the progression of heart failure due to cardio-renal syndrome.[23-25]

In the present study, the E/e′ ratio for predictive mortality was 80.0%, the specificity was 92.8%, the positive predictive value was 28.5%, and the negative predictive value was 92.852%. Whereas in the study of Kim et al., E/e′ ratios for predictive mortality had 72.3% specificity.[26] The E/e′ ratio might be used well as a non-invasive technique to provide early evaluation. This study showed an independent correlation between GLS and all-cause mortality in patients with CKD and showed that the influence of GLS on survival is additive to established prognostic factors such as E/e' and LVEF. Numerous prospective and observational research on heart failure, myocardial infarction, and cardiomyopathy in general populations. Prognostic usefulness and better risk categorization of GLS over EF have been found in studies.[27-30] In a recent study, the biochemical assessment of the N-terminal propionimite natriuretic peptide and EF was not as effective in predicting in-hospital heart failure as GLS.[31] The study involved the assessment of 548 individuals with acute MI within 48 hours of admission. These researchers have also demonstrated the independent predictive utility of GLS in predicting CV mortality and HF in patients with preserved EF. According to a research by Krishnaswamy et al., among high-risk patients with advanced CKD who had maintained EF, a lower GLS was associated with a 5.6-fold increased risk of CV mortality.

Ternacle et al. found that 40% of patients with sustained EF (defined as 50%) who were undergoing pre-operative examination for cardiac surgery had an abnormal GLS (defined as >-16%). The function of GLS represents subendocardial longitudinal myocardial fibres, which are more vulnerable to higher wall stress and lower coronary perfusion.[32,33,34] GLS represents alterations in the myocardial interstitium, including the degree of myocardial fibrosis, in addition to providing a quantitative evaluation of cardiac function.[35] Animal models have demonstrated that, following equivalent cardiac stresses, early subendocardial changes are significantly worse in CKD rats compared to non-CKD rats, indicating that CKD is a unique risk factor for cardiac remodelling. There is evidence that CKD-specific abnormalities like hyperuricemia, abnormal bone mineral metabolism, pressure overload, and volume overload are what are responsible for these molecular changes.[36,37,38] There has been no discernible variation in GLS readings between the two investigations concerning hemodialysis scheduling.[39] But it has been demonstrated that GLS is sensitive to loading circumstances, particularly afterload.[40] There should be more research on the GLS measurement variation among dialysis patients due to loading conditions. However, in CKD patients, GLS may provide better early identification of LV dysfunction.

It has frequently been shown that LV-GLS, as evaluated by echocardiography, is an independent predictor of mortality in those with chronic kidney disease. Dialysis patients and patients with CKD Stages 4–5D, as well as 3B–5D patients, have demonstrated correlations. The high prevalence of heart failure with intact ejection fraction in ESKD groups lends support to the idea that LV-GLS is a superior method for measuring cardiac function in CKD patients than LVEF.

Previous studies have demonstrated that reduced LVEF occurs late in the development of uremic cardiomyopathy.[41,42] This is probably due to the different aspects of cardiac function that the two methods assess.

The function of subendocardial fibres is assessed by LV-GLS, which has a stronger correlation with the level of interstitial myocardial fibrosis, while LVEF just assesses the volume difference at the end of diastole and systole.[43] The current study included 28 patients with LVEF >50%; their mean LVEF was 56.42%. Of the patients, 26 had a mean LVEF of 52.05% and 2 died during the trial. At the conclusion of the trial, there was a 7% reduction in LVEF; however, this shift in LVEF reduction was not statistically significant when compared to an LVEF <50%.

Of the 194 patients with preserved LVEF (>50%) in the Rankin et al. trial, 112 (58%) exhibited aberrant LV-GLS, defined as >−16% (a threshold selected based on the normal LV-GLS in healthy participants being −20 ± 4%).[44] In spite of the relatively low frequency of heart failure, this might help to explain some of the severe cardiovascular risk observed in CKD patients. Thus, there would be a case to look into cardiovascular therapies, particularly for individuals with ESKD who have poor LV-GLS and those with antifibrotic qualities (e.g., mineralocorticoid receptor antagonists). Prior research on ESKD populations found that mineralocorticoid receptor antagonists had no effect on LVMI; however, LV-GLS was not measured.[45] We think these trials would be quite interesting because of the high frequency of events that are anticipated and the high incidence of compromised LV-GLS in ESKD groups.

According to Ranken et al., it is well acknowledged that men and women have different LV-GLS. After controlling for gender in the multivariable model, it was discovered that LV-GLS had an independent relationship with mortality. Further research is necessary to confirm the increased predictive capacity of LV-GLS in women as opposed to males, as shown by the Ranken et al. study. This is partially because individuals with established significant LV systolic dysfunction were not included in the aggregated trials' entry criteria. On the other hand, it is remarkable that LV-GLS was linked to death even in cases where the great majority of patients did not have heart failure. The long follow-up time with high overall mortality and the established effect of kidney transplantation on survival are two of the many factors contributing to the lack of relationship. But the ROC analysis's inability to identify a precise cutoff point for LV-GLS in terms of mortality prediction suggests that LV-GLS by itself is not likely to be a reliable prognostic indicator. Our study lacks subgroup analysis, but LV-GLS showed superior prognostic markers in predicting mortality in impaired renal function, which is consistent with the literature findings.

However, because of a few limitations, the study's findings should be interpreted with caution. Specifically, the very small sample numbers in each group precluded us from doing a subgroup analysis based on CKD stages or dialysis modality. The predictive significance of GLS presented here may be restricted to the equipment used in this investigation since inter-vendor variability might alter GLS readings. We were unable to detect inducible ischemia as one of the mortality predictors using resting echocardiography. The current study concluded by showing a correlation between GLS and all-cause mortality in renal disease patients.

CONCLUSION:

When compared to ejection fraction, left ventricular GLS is a better indicator of morbidity, all-cause and cardiovascular mortality in patients with advanced chronic kidney disease receiving haemodialysis. Haemodialysis of symptom-free heart failure patients with preserved ejection fraction also showed diastolic dysfunction and deteriorated GLS. For individuals who have maintained EF, GLS and E/e' has an additional prognostic value. Even in patients with maintained LVEF, it is imperative to suggest the use of GLS and E/e' calculation as a diagnostic and prognostic tool to understand myocardial dysfunction early .since 2D-ECHO-GLS. E/e' values are more sensitive approach for diagnosing LVSD than LVEF. With systolic and diastolic myocardial function measurement, a correct diagnosis is becoming more and more crucial in this kind of patient with ESRD, providing integrated, less expensive, and non-invasive information.

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