Original Article

Left Ventricular Strain: A Reliable Predictor of Short-Term Outcomes in Patients with Anterior Wall Myocardial Infarction without Heart Failure

Abstract

Background: Left ventricular ejection fraction (LVEF) is a key determinant in decision-making after acute myocardial infarction (MI). Little is known of its relationship with left ventricular Strain and N-Terminal fragment of pro-B-type Natriuretic Peptide (NT-pro-BNP) following acute anterior wall MI (AWMI). **Materials and Methods:** We conducted a prospective cohort study of patients with a diagnosis of acute AWMI and the absence of overt heart failure (HF). Assessment of LVEF, strain parameters on echocardiography was done, and NT-pro-BNP levels were obtained. Follow-up for adverse cardiac events was done for 30 days postdischarge. Correlation of LVEF and NT-pro-BNP with various strain parameters were ascertained. **Results:** Of the total of 50 patients of AWMI enrolled, the mean LVEF in the study was 43.46 ± 3.72%.Eleven patients (22%) had adverse events at 30 days of follow-up. Patients with adverse events had significantly higher overall peak systolic longitudinal strain (PSLS), lower mid-region peak systolic longitudinal velocity (PSLV), and basal region PSLV. A significant negative correlation was observed between LVEF and mean Peak PSLS of combined apical plus mid regions of the left ventricle ($r = -0.700$). Log10-NT-pro BNP also showed a strong negative correlation with overall PSLV ($r = -0.792$) as well as regional PSLV values of combined apical plus mid ($r = -0.763$) and basal segments ($r = -0.748$). **Conclusions:** In patients with AWMI without HF, PSLS and PSLV are good predictors of adverse outcomes at 30-day follow-up. Furthermore, NT-pro BNP can also be an indirect predictor of strain parameters on echocardiography.

Keywords: *Echocardiography, heart failure, left ventricular strain, natriuretic peptides, peak systolic longitudinal velocity*

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Received: 23 October 2018
Revised: 30 May 2020
Accepted: 3 August 2020
Published: 28 November 2020

Access this article online
Website: www.advbiores.net
DOI: 10.4103/abr.abr_213_18
Quick Response Code:

Introduction

ST-elevation myocardial infractions (STEMI) impose huge morbidity and mortality burden on health systems.[1] Among them, acute anterior wall MI (AWMI's) are known to have poorer outcomes both in terms of in-hospital mortality and long-term survival. Therefore, risk assessment of these patients is of paramount clinical importance, both from management as well as prognostic point of view. Currently, risk stratification of MI is based primarily on clinical history, electrocardiography changes, biochemical markers of myocardial injury, and echocardiographic assessment.

The N-terminal fragment of pro-B-type Natriuretic Peptide (NT-pro-BNP) has been studied extensively as a biomarker of severity and outcome of heart failure (HF) and mortality associated with acute myocardial infarction (AMI).[2,3] Secreted predominantly from the ventricular cardiomyocytes in response to increased wall tension, NT-proBNP is significantly increased after AMI and is an independent predictor of survival over the next 2 years.[4,5] Plasma NT-proBNP levels increase with age and have an inverse correlation with left ventricular ejection fraction (LVEF) with a negative predictive value of 98% in identifying LVEF ≤40%.[6] However, routine measurement of NT-proBNP has yet to be incorporated into the guidelines for the acute coronary syndrome (ACS). Some studies have even demonstrated that NT-proBNP measured at the time of hospitalization for MI tends to correlate with infarct size measured through magnetic resonance imaging on follow-up (for 4 and 12 months after AMI).[7,8]

Measurement of myocardial strain and strain rate (SR) allows for the evaluation of myocardial deformation and hence the assessment of the systolic function

How to cite this article: Singh BR, Sethi R, Jain N, Chaudhry G, Saran M, Mishra O, *et al.* Left ventricular strain: A reliable predictor of short-term outcomes in patients with anterior wall myocardial infarction without heart failure. Adv Biomed Res 2020;9:67.

of the ventricular myocardial fibers. Even subtle changes in the measurement of either is suggestive of myocardial dysfunction.[9,10] In fact, the longitudinal fibers in the sub-endocardial layer are very sensitive to ischemia and wall stress and thus can exhibit abnormal contractile features, even in the presence of an apparently normal LVEF.[11] Thus, longitudinal strain estimation through echocardiography allows for an early window, and hence, a more sensitive method of identifying subclinical LV systolic dysfunction compared to the traditional technique of LVEF, as assessed using Simpson's method.[12-14] However, our knowledge regarding the relationship between these echocardiographic parameters and biochemical markers in patients without clinically apparent HF is limited.[12,15-19] Hence, we aim to establish a correlation between LVEF, LV strain parameters, and NT-pro BNP in patients of AWMI without clinically overt HF.

Materials and Methods

Study design

The present study was conducted at a tertiary care cardiology center in India. It was a prospective cohort study of 3 months duration, in which a total of 50 cases of AWMI were studied. AWMI patients were diagnosed as per the American College of Cardiology/American Heart Association for diagnosis and management STEMI.[1] Patients admitted to the intensive coronary care unit with a diagnosis of AWMI <5 days old (irrespective of their revascularization status) and age <75 years were enrolled for inclusion. Written and informed consent were obtained from each subject. Patients with AWMI who had clinical signs and symptoms of overt HF such as basal rales raised jugular venous pressure, dyspnea, orthopnea, acute left ventricular (LV) failure and Killip class >2 were excluded. Also excluded were those AWMI patients with uncontrolled arrhythmias (bradyarrhythmia/tachyarrhythmia), prior ACS, structural heart diseases, renal failure, or any chronic debilitating conditions and those not giving consent. Following discharge from the hospital, the patients were then followed up over 30 days through scheduled outpatient department visits and telephonic updates to record the occurrence of any adverse cardiac events. The primary end-point (a composite of HF, MI, and death) was studied with respect to LVEF, NT-pro-BNP, and LV strain parameters. In addition, in group comparison of NT-ProBNP, LVEF, and LV strain parameters were done among those who had primary endpoint events on follow vis-à-vis those who did not. The study was approved by the Institutional Ethics Committee and funded under the Intramural Short-Term Medical Research Fellowship program, conducted by the Research Cell, KGMU.

NT-pro BNP measurement

Peripheral samples of plasma were obtained within 24 h of echocardiographic assessment. Measurement and quantitative analysis of NT-pro BNP were performed on the commercially available COBAS e 411 immunoassay analyzer, immediately after blood sampling.

Standardized normal values as defined by COBAS for Elecsys® NT-proBNP are shown in Figure 1.

Echocardiographic assessment

Two-dimensional M-mode and tissue Doppler echocardiographic examinations were performed within 24 h of admission on all participants. The echocardiographic data were acquired with a commercially available digital ultrasound machine (Vivid 7, Vingmed; GE Healthcare, Horten, Norway) using a 3.5-MHz phased array transducer. The measurements were made according to previously published guidelines.[20] Three heart cycles of the apical 4-, 3-, and 2-chamber views were captured in conventional two-dimensional and color tissue Doppler modes. The frame rate was >100/s for Tissue Doppler imaging. Seventeen segments of the LV were used for all analyses. Offline analysis was conducted by an expert cardiologist. In the anteroseptal wall of the LV, the basal, mid, and apical regions were subjected to measurement of the peak systolic longitudinal velocities (PSLV) (cm/s). Then, the peak systolic longitudinal strain (PSLS) (%) and the PSLS rates (PSLSR) (s^{-1}) were calculated. Finally, the mean PSLV, PSLS, and PSLSR of the three regions were calculated to be used in the study.

The LVEF was assessed by the biplane Simpson's rule.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 20.0 (SPSS Inc., Chicago, IL, USA). Independent samples *t*-test was used to compare the data between groups. Correlation of different continuous parameters was studied using the Pearson correlation coefficient. Receiver-operator curve analysis was performed to deduce a cutoff value of different parameters showing significant association with adverse cardiac events. A $P < 0.05$ was considered to indicate a statistically significant association.

Results

For the 50 patients included in the study, the age of patients ranged from 28 to 71 years, with the mean age being 52.36 ± 9.70 years. Most of the patients (92%)

Patient Age (Years)	NT pro BNP Values (pg/ml)		
< 50 50-75 >75	< 300	300-450 300-900 300-1800	> 450 > 900 >1800

Figure 1: Age standardized normal and abnormal values of NTpro BNP.[as defined by Elecsys assay. The values in right column represent normal and indicate that HF is unlikely.The values on left column are abnormal and indicate HF is likely. The middle column represents grey zone and need for imaging to conform the diagnosis of HF.

were male. LVEF values ranged from 37% to 58%, with a mean value of 43.46 ± 3.72%. NT-proBNP values had a wide range starting from 288.6 to 31,843 pg/ml, thereby showing a highly skewed distribution. To address this issue, instead of absolute values of NT-proBNP, logarithmic scale ($\log_{10}$) values of NT-proBNP were calculated, which were confined to a rather narrow range starting from 2.46 to 4.50 and a mean value of 3.51 ± 0.55. The distribution of $\log_{10}$ NT-proBNP values was rather normalized. While calculating average values for all three segments together, PSLV ranged from 0.53 to 5.28 m/s with a mean value of 2.41 ± 1.02 m/s, PSLS values ranged from − 22.53 to −1.84% with a mean value of − 10.27 ± 4.59%, while PSLSR ranged from −1.31 to −0.08/s with a mean value of −0.80 ± 0.27/s.

However, when taking the apical and mid segments together, PSLV values ranged from 0.22 to 4.25 m/s with a mean of 1.83 ± 0.93 m/s, PSLS values ranged from − 16.75 to − 0.85% with a mean of − 6.87 ± 3.66% and PSLSR values ranged from − 1.15 to 0.80/s with a mean of − 0.53 ± 0.30/s. On the other hand, for the basal segment alone, PSLV values ranged from 1.15 to 7.34 m/s with a mean of 3.37 ± 1.37 m/s, PSLS values ranged from − 36.10 to − 3.10% with a mean of − 17.06 ± 7.94% and PSLSR values ranged from − 3.04 to − 0.45/s with a mean of − 1.34 ± 0.55/s [Table 1].

Post 30-day follow up, out of 50 subjects included in the study, 39 (78%) did not experience any adverse cardiac event. Of the remaining 11 (22%), there were seven repeat hospitalizations (5 for HF and 2 for MI) and 4 deaths.

Table 1: Baseline study parameters of the patients enrolled in the study (*n*=50)

Characteristic	Mean±SD (range)
Age (years)	52.36±9.70 (28-71)
Gender, *n* (%)	
Male	46 (92.0)
Female	4 (8.0)
LVEF (%)	43.46±3.72 (37-58)
$\log_{10}$ NT-proBNP	3.51±0.55 (2.46-4.50)
PSLV (m/s)	2.41±1.02 (0.53-5.28)
PSLS (%)	−10.27±4.59 (−22.53–−1.84)
PSLSR (/s)	−0.80±0.27 (−1.31-0.08)
Apical + mid PSLV (m/s)	1.93±0.93 (0.22-4.25)
Apical + mid PSLS (%)	−6.87±3.65 (−16.86–−0.85)
Apical + mid PSLSR (/s)	−0.53±0.30 (−1.15-0.80)
Basal PSLV (m/s)	3.37±1.36 (1.15-7.34)
Basal PSLS (%)	−17.06±7.94 (−36.10–−3.10)
Basal PSLSR (/s)	−1.34±0.55 (−3.04–−0.45)

LVEF: Left ventricular ejection fraction, NT-proBNP: N-terminal fragment of pro B-type natriuretic peptide, PSLV: Peak systolic longitudinal velocities, PSLS: Peak systolic longitudinal strain, PSLSR: Peak systolic longitudinal strain rate, SD: Standard deviation

The mean age of patients suffering adverse events was significantly higher (59.82 ± 7.28 years) as compared to that of patients who did not experience an adverse event (50.26 ± 9.31 years) (P = 0.003). Patients experiencing adverse cardiac events had significantly lower mean LVEF (P < 0.001) and PSLV (P = 0.002) and higher mean Log_{10} NT-proBNP (P < 0.001) values as compared to those who remained event-free during the 30-day follow-up. Mean PSLS and PSLSR values were also more negative in the event free group; however, the difference was statistically significant only for PSLS (P = 0.002) [Table 2].

Among mid-segment parameters, PSLV was found to be significantly lower in patients with adverse events as compared to those not having adverse events (P = 0.005), whereas mean PSLS was significantly higher in cases having adverse events as compared to those not having adverse events (P < 0.001). There was no significant difference between the two groups with respect to PSLSR. Similar to mid-segment parameters, for the basal segment too, PSLV value was significantly lower in cases having adverse events as compared to those not having adverse events, whereas PSLS was significantly higher (less negative) in cases having adverse events as compared to those not having adverse events. No statistically significant difference was observed between the two groups with respect to PSLSR [Table 3].

Correlation between the various variables was calculated and a strong negative correlation was observed between LVEF with apical + mid PSLS (r = −0.700), Log_{10} NT-proBNP with PSLV (r = −0.792), apical + mid PSLV (r = −0.763), and basal PSLV (r = −0.748). While a strong positive correlation was found to exist between Log_{10} NT-proBNP with PSLS (r = 0.700) and apical + mid PSLS (r = 0.778) [Figure 2].

The receiver operating characteristic curves were constructed to determine the optimal cutoff values for the parameters included in our study at predicting clinical events at the end of 1 month.

For different parameters being evaluated, $\log_{10}$ NT-proBNP and LVEF had the maximum area under curve (AUC) values (0.904 and 0.939), whereas age had minimum AUC (0.789). For LVEF, underbalanced considerations, a cut-off value < 42.5 was projected to be 90.9% sensitive and 76.9% specific whereas for $\log_{10}$ NT-proBNP under balanced considerations, a cut-off value > 3.78 was 90.9% sensitive and 87.2% specific. For PSLV and PSLS under balanced considerations, the cut-off values ≤ 1.875 and ≤−8.867 had a sensitivity of 81.8% and specificity of 82.1% and 79.5%, respectively. For the apical + midsegments together, under balanced conditions, the sensitivity value was 81.8% for both PSLV as well as PSLS, whereas specificity value was 69.2% for PSLV and

Table 2: Comparison of baseline study parameters between patients experiencing adverse cardiac events and those not experiencing adverse events

Parameter	Mean±SD		Statistical significance	
	Adverse cardiac event (*n*=11)	No adverse cardiac event (*n*=39)	*t*	*P*
Age	59.82±7.28	50.26±9.31	3.137	0.003
LVEF	39.82±2.14	44.49±3.42	−4.274	<0.001
Log_{10} NT-proBNP	4.17±0.27	3.32±0.46	5.859	<0.001
PSLV	1.57±0.60	2.64±1.00	−3.367	0.002
PSLS	−6.60±2.65	−11.30±4.51	3.283	0.002
PSLSR	−0.67±0.18	−0.84±0.29	1.844	0.071
Apical + mid PSLV	1.25±0.61	2.12±0.91	−2.936	0.005
Apical + mid PSLS	−3.58±2.00	−7.80±3.49	3.831	<0.001
Apical + mid PSLSR	−0.46±0.21	−0.55±0.32	0.890	0.378
Basal PSLV	2.21±0.69	3.69±1.34	−3.528	0.001
Basal PSLS	−12.66±5.16	−18.30±8.19	2.156	0.036
Basal PSLSR	−1.09±0.37	−1.42±0.58	1.753	0.086

Baseline study parameters of the two groups were compared using independent t-test. LVEF: Left ventricular ejection fraction, NT-proBNP: N-terminal fragment of pro B-type natriuretic peptide, PSLV: Peak systolic longitudinal velocities, PSLS: Peak systolic longitudinal strain, PSLSR: Peak systolic longitudinal strain rate, SD: Standard deviation

Table 3: Receiver-operator curve analysis for deducing cutoff values of different study parameters* for prediction of adverse cardiac event

Parameter	AUC	Consideration	Cut-off value	Predicted Sensitivity (%)	Predicted Specificity (%)
Age	0.789	High sensitivity	≥51.0	81.8	56.4
		High specificity	≥59.0	36.4	82.1
		Balanced	≥54.5	63.6	61.5
LVEF	0.904	High sensitivity	≤43.5	100	64.1
		High specificity	≤41.5	72.7	87.2
		Balanced	≤42.5	90.9	76.9
Log_{10} NT-proBNP	0.939	High sensitivity	≥3.73	100.0	84.6
		High specificity	≥4.01	72.7	94.9
		Balanced	≥3.78	90.9	87.2
PSLV	0.834	High sensitivity	≤2.785	90.9	43.6
		High specificity	≤1.688	72.7	87.2
		Balanced	≤1.875	81.8	82.1
PSLS	0.851	High sensitivity	≤−9.135	100.0	76.9
		High specificity	≤−7.283	45.5	84.6
		Balanced	≤−8.867	81.8	79.5
Apical + mid PSLV	0.766	High sensitivity	≤1.575	90.9	64.1
		High specificity	≤1.110	36.4	92.3
		Balanced	≤1.520	81.8	69.2
Apical + mid PSLS	0.858	High sensitivity	≥−6.35	100.0	66.7
		High specificity	≥−3.88	54.5	87.2
		Balanced	≥−5.90	81.8	74.4
Basal PSLV	0.848	High sensitivity	≤3.24	100.0	66.7
		High specificity	≤2.54	72.7	84.6
		Balanced	≤2.825	81.8	76.9
Basal PSLS	0.717	High sensitivity	≥−19.95	100.0	43.6
		High specificity	≥−13.00	54.5	76.9
		Balanced	≥−15.35	72.7	61.5

*Only those parameters were included that had shown a significant association with adverse event. LVEF: Left ventricular ejection fraction, NT-proBNP: N-terminal fragment of pro B-type natriuretic peptide, PSLV: Peak systolic longitudinal velocities, PSLS: Peak systolic longitudinal strain, PSLSR: Peak systolic longitudinal strain rate, AUC: Area under curve

74.4% for PSLS. For basal values of PSLV and PSLS, under balanced conditions, sensitivity was 81.8% and 72.7%, respectively, whereas specificity was 76.9% and 61.5%, respectively [Figure 3].

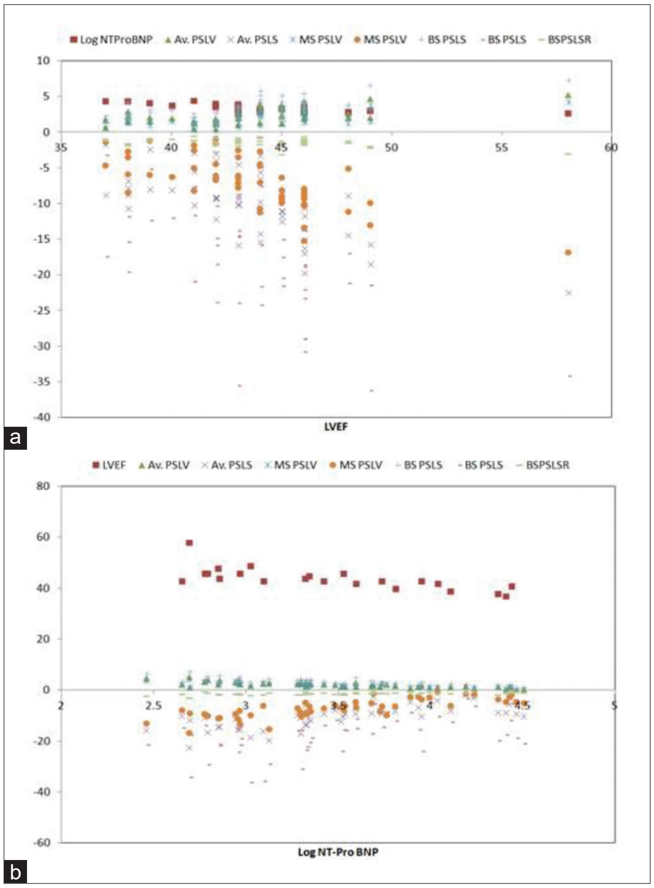

Figure 2: Scatterplot showing Correlation of (a) left ventricular ejection fraction and (b) log10 NT-proBNP with Left ventricular ejection fraction, log10 NT-proBNP, Av. peak systolic longitudinal velocity and peak systolic longitudinal strain, Apical + Mid peak systolic longitudinal velocity and peak systolic longitudinal strain, Basal peak systolic longitudinal velocity, peak systolic longitudinal strain, and peak systolic longitudinal strain R

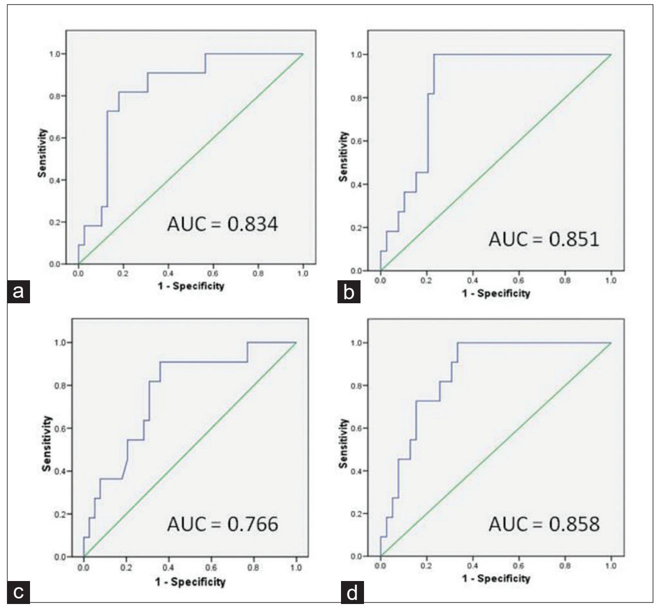

Figure 3: Receiver operator curve analysis as a predictor of the adverse cardiac event for (a) mean peak systolic longitudinal velocity (b) mean peak systolic longitudinal strain (c) Apical + mid-segment peak systolic longitudinal velocity (d) apical + mid segment peak systolic longitudinal strain

Discussion

Our study demonstrated that the longitudinal strain (expressed as PSLV and PSLS) has a significantly stronger relationship to increased cardiac wall stress (expressed as a rise in levels of NT-pro BNP) than LVEF, which rather has a moderately significant correlation, in patients of AWMI without HF.

While most studies done in the past used global longitudinal strain (GLS) for the assessment of myocardial longitudinal function, our study instead utilizes the mean of longitudinal strain measures of the three individuals (basal, mid, and apical) segments. The relationship between Longitudinal Strain and B-type natriuretic peptide has been described previously by various authors.[19,21-24] An echocardiographic sub-study of the VALIANT trial has revealed that longitudinal strain correlates with prognosis (all-cause mortality) independent of LVEF.[25] In a large community based cohort study, a significant correlation was found between PSLV (measured by TDI) and NT-pro BNP levels.[26] These findings were confirmed in a smaller cohort of patients with suspected HF, where longitudinal velocity predicted BNP and subsequently, a diagnosis of HF.[27] Hence, the results of our study do show concordance with previous studies, with respect to the point that longitudinal strain is a more reliable predictor of NT-proBNP levels and hence wall stress than LVEF.

A potential explanation for the above-mentioned results can be attributed to the point that myocardial strain assessment will predict early myocardial dysfunction (of subendocardial layers) in contrast to a fall in LVEF, which comparatively appears to be a cruder marker. Hence, it will provide an early window for optimization of therapy before frank HF sets in. There is also rapid induction of BNP gene expression in the surrounding nonischemic myocardium, in addition to the peri-infarct zone, which has been demonstrated in animal experiments.[27] LVEF rather tends to have poor sensitivity in reflecting the function of these areas. Hence, it is less accurate in detecting the wall stress in the subendocardial layers of LV. These findings, along with the fact that subendocardial longitudinal fibers are especially sensitive to ischemia,[11] lend explanatory support to the findings in our study.

While comparing the different parameters between the cases experiencing adverse cardiac events and the event-free group, LVEF and mean PSLV were found to be significantly lower in the cases with adverse cardiac events, whereas NT-proBNP and mean PSLS were found to be significantly higher. The information obtained on analyzing strain parameters of basal, mid, and apical regions separately was comparable to that obtained by average strain readings in our study. Hence, segmental analysis for the strain pattern of LV may not be of any additional benefit. In the present prospective study, apart from NT-proBNP and LVEF, which have emerged as good predictors, we also have been able to demonstrate PSLS as an independent predictor of adverse cardiac events (hospitalization for MI or worsening HF and death). However, standardization of these values requires larger studies.

Study limitations

Our study was limited by a small sample size and a shorter follow-up. Inclusion of revascularization status of patients and repeat strain analysis on follow-up would have been more informative. Because, our enrollment was restricted to de novo cases of AWMI, our echocardiographic assessment was confined to anteroseptal wall of LV. Silent infarctions in other territories could have led to LVEF alterations, but since the population was relatively young, the contributions are less likely but cannot be ruled out. Owing to the relatively broad range of LVEF in the study, further research with a larger sample size could throw light on the consistent correlation of GLS and adverse outcomes in various subgroups of LVEF. The use of tissue Doppler imaging for the computation of strain is subject to high operator variability. Speckle tracking echocardiography, which offers angle independent analysis of tissue motion deformation, is a more superior technique.[28,29]

Conclusions

Apart from NT-proBNP and LVEF, PSLS, and PSLV are good predictors of adverse outcomes at 30-day follow-up and may further contribute to risk stratification of these patients, especially by providing an early window for intervention. Furthermore, aside from being a good prognostic marker, NT-proBNP can also be used as an indirect predictor of myocardial longitudinal strain and velocity. Larger long-term studies are required to validate these findings.

Acknowledgment

Grant support was provided under the Intramural Short-Term Medical Research Fellowship program of King George's Medical University, Lucknow, Uttar Pradesh, India.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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