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ORIGINAL ARTICLE
Imaging

Tissue Mitral Annular Displacement in Patients With Myocardial Infarction
— Comparison With Global Longitudinal Strain —

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Background: Global longitudinal strain (GLS) can predict prognosis after myocardial infarction (MI). Tissue mitral annular displacement (TMAD) is another index of longitudinal left ventricular deformity, and is less dependent on image quality than GLS. We investigated the relationship between TMAD and GLS, and their ability to predict outcomes after MI.

Methods and Results: GLS and TMAD were measured on echocardiograms 2 weeks after MI in 246 consecutive patients (median age 62 years, 85.7% male). TMAD was measured from apical 4- and 2-chamber views ($TMAD_{4ch}$ and $TMAD_{2ch}$, respectively), and a mean value ($TMAD_{av}$) was calculated. $TMAD_{4ch}$, $TMAD_{2ch}$, and GLS were successfully measured in 240 (97.5%), 210 (85.3%) and 214 patients (87.0%), respectively. All TMAD parameters were significantly correlated with GLS (R=0.71–0.75) and left ventricular ejection fraction (LVEF; R=0.48–0.53). TMAD parameters were weakly correlated with peak creatine kinase (CK; R=0.20) and CK-MB (R=0.21–0.25). GLS and $TMAD_{av}$ were significantly associated with LVEF after 6 months (R=0.48–0.53) and all-cause mortality during the follow-up period (median 1,242 days). $TMAD_{av}$ discriminated patients with higher all-cause mortality when patients were divided into 3 groups, namely upper 25%, middle range, and lower 25% of $TMAD_{av}$ (P=0.041, log-rank test). GLS detected high-risk patients using 15.0% as a cut-off value.

Conclusions: TMAD could be a simple and reliable alternative to GLS for predicting outcomes in patients with MI.

Key Words: Global longitudinal strain; Mitral annular displacement; Myocardial infarction; Speckle tracking

Left ventricular (LV) systolic function is a major determinant of prognosis in patients with myocardial infarction (MI). LV ejection fraction (LVEF) is associated with morbidity and mortality after MI,[1,2] and guidelines recommend its measurement in patients with ST-elevation myocardial infarction (STEMI).[3,4] However, LVEF measured on 2-dimensional (2D) echocardiography (2DE) has limited reliability.[5,6] Longitudinal myocardial strain measured by 2D speckle tracking echocardiography (2DSTE) is a new index of longitudinal deformity of the LV. Global longitudinal strain (GLS), an average of segmental longitudinal strain, is an index of LV systolic function that is less dependent on the operator and more reproducible than LVEF.[7,8] GLS is well associated with infarct size[9–11] and microvascular obstruction after primary percutaneous coronary intervention (PCI),[12,13] and has better predictive value than LVEF,[14,15] in patients with MI. GLS also detects small systolic dysfunction[16] and is associated with prognosis,[14] even in patients showing normal to moderately reduced LVEF after MI.

However, some technical issues may limit the use of GLS in daily practice. Standard 3 apical images (apical long axis, 4-chamber, and 2-chamber views) are required to assess GLS, which may be time-consuming in a busy clinical situation. The accuracy of GLS is affected by the quality of all apical images, and suboptimal images could lead to incon-

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Table 1. Intra- and Interobserver Agreements of Tissue Mitral Annular Displacement and Global Longitudinal Strain Measurements

	Intraobserver agreement		Interobserver agreement	
	ICC	95% CI	ICC	95% CI
$TMAD_{4ch}$	0.97	0.90–0.99	0.85	0.45–0.96
$TMAD_{2ch}$	0.97	0.90–0.99	0.75	0.26–0.93
GLS	0.96	0.87–0.99	0.97	0.89–0.99

Intraclass correlation coefficients (ICC) were calculated using values measured twice by the same observer (intraobserver agreement) and by 2 independent observers (interobserver agreement) in 10 randomly selected cases. CI, confidence interval; GLS, global longitudinal strain; $TMAD_{4ch}$ and $TMAD_{2ch}$, tissue mitral annular displacement measured on images from apical 4- and 2- chamber views, respectively.

clusive studies.[17,18]

For patients with suboptimal image quality, alternative indices of longitudinal LV deformity that are less dependent on image quality are recommended.[19] Mitral annular plane systolic excursion (MAPSE), longitudinal movement of the mitral annular plane assessed by M-mode echocardiography, is one such index.[20] MAPSE is well correlated with GLS not only in healthy populations,[21,22] but also in patients with a history of MI.[23] However, MAPSE is dependent on the insonation angle, which may lead to inaccurate measurement. Tissue mitral annular displacement (TMAD) is a unique echocardiography technique that assesses longitudinal displacement of the mitral annulus using 2DSTE.[24,25] TMAD is well correlated with LVEF,[24,25] and is considered a rapid and accurate index of longitudinal LV contraction. TMAD is similar to MAPSE but is not angle dependent, and semiautomatic measurement yields low intra- and interobserver variability.[24] TMAD could be less dependent on image quality than GLS because the mitral annulus is an easily detectable, echo-dense structure. TMAD could be obtained using an image only from an apical 4- or 2-chamber view, which would make it less time-consuming than GLS. Conversely, TMAD may be affected by local wall motion abnormality, and its feasibility in patients showing asynergy after MI has not been fully elucidated. In the present study we investigated whether TMAD could be an alternative to GLS in patients with MI, particularly for the prediction of functional and clinical outcomes.

Methods

Study Population

In all, 422 consecutive patients with acute MI admitted to Sakurabashi Watanabe Hospital between January 2007 and September 2012 were registered in the prospective multicenter Osaka Acute Coronary Insufficiency Study (OACIS) Registry (University Hospital Medical Information Network [UMIN] Clinical Trials Registry ID: UMIN000004575). Diagnostic criteria of acute MI in the OACIS Registry have been reported elsewhere.[26,27] Briefly, ≥2 of the following criteria were required for diagnosis: (1) a clinical history of central chest pressure, pain, or tightness lasting >30 min; (2) ST segment elevation >0.1 mV in at least 1 standard or 2 precordial leads; and (3) an increase in serum creatinine kinase (CK) to more than twice the normal laboratory value. Of these 422 patients, 290 patients who underwent echocardiography 2 weeks after the onset of MI using an iE33 (Philips Healthcare, Andover MA, USA) were enrolled in the present study. Patients were excluded if: (1) primary PCI for an occluded or stenosed culprit vessel was not attempted during the acute phase of MI; (2) they had an arrhythmia disturbing GLS and TMAD measurement, such as atrial fibrillation and multiple extra beats; (3) they underwent incomplete echocardiographic study or their images were not stored; and (4) they had poor image quality that rendered the images unsuitable for analysis.

All clinical and laboratory data were obtained from the OACIS Registry data and from the medical records of Sakurabashi Watanabe Hospital. Estimated glomerular filtration rate (GFR) was determined at the time of hospital admission and discharge using the Modification of Diet in Renal Disease (MDRD) equation modified for the Japanese population.[28] Information on subsequent clinical events up to 5 years was gathered by investigators by visiting outpatient clinics or by verbal or written blinded review of the circumstances surrounding each death.

This study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Sakurabashi Watanabe Hospital (Reference no. 17-32). One of the investigators obtained informed consent from each patient before they were included in the study.

Echocardiography Examinations

Standard 2D echocardiography was performed with an iE33 at 2 weeks and 6 months after the onset of MI. An experienced echocardiographer blinded to the clinical data analyzed stored images using Q-station software (Philips Healthcare). LVEF was measured using the Auto-EF function on the Q-station, which automatically detects the LV endocardial border and measured LVEF from apical 4- and 2-chamber view images based on Simpson's rule. All parameters were measured in duplicate and averaged.

Segmental longitudinal strain was measured using stored images from apical long axis, 4-chamber, and 2-chamber views.[19] The end-systolic frame was defined in the apical long-axis view and aortic valve closure was identified. The closure of the aortic valve was marked, and the Q-station software measured the time between the R-wave and aortic valve closure, which was used as a reference for the other view loops. We manually defined the mitral annulus and left ventricular apex with 3 index points at the end-systolic frame in each apical image. The Q-station software automatically traced 3 concentric lines on the endocardial border, mid-myocardial layer, and epicardial border, and followed the endocardium from this single frame throughout the cardiac cycle. If the automated tracking was inappropriate by visual assessment, we manually adjusted the

Table 2. Patient Characteristics	
Age (years)	62 [54–71]
Male sex	211 (85.7)
BMI (kg/m²)	24.1 [22.3–26.4]
Hypertension	171 (69.5)
Dyslipidemia	190 (77.2)
Diabetes	96 (39.0)
Smoking	155 (63.0)
History of prior MI	40 (16.3)
STEMI	215 (87.3)
Anterior AMI	82 (33.3)
eGFR (mL/min/1.73 m²)	
At admission	66.4 [52.3–82.0]
At discharge	61.7 [49.1–73.8]
Peak CK (IU/L)	2,038 [938–4,045]
Peak CK-MB (IU/L)	136 [67–269]
Medication at discharge	
Antiplatelet agents	240 (97.6)
β-blockers	173 (70.3)
ACEI	134 (54.4)
ARBs	89 (36.2)
CCBs	39 (15.9)
Diuretics	38 (15.4)
Statins	178 (72.4)

Data are given as n (%) or the median [interquartile range]. ACEI, angiotensin-converting enzyme inhibitor; AMI, acute myocardial infarction; ARBs, angiotensin receptor blockers; BMI, body mass index; CCBs, calcium channel blockers; CK creatine kinase; CK-MB, creatine kinase myocardial band; eGFR estimated glomerular filtration rate; MI, myocardial infarction; STEMI, ST-elevation myocardial infarction.

region of interest (ROI). The LV in each apical image was divided into 6 segments, and the tracking quality for each segment was validated by the operator. The software measured the percentage wall lengthening and shortening and calculated peak systolic longitudinal strain for each segment, and the results of all 3 planes were combined into a single bull's eye plot based on a 17-segment model. GLS was automatically calculated as an averaged value of peak longitudinal strain in all segments. GLS was expressed in terms of absolute values in the present study.[29]

TMAD was measured on the same apical 2- and 4-chamber images using Q-station software. We placed 2 ROIs on the mitral annulus and 1 on the apex. The movement of each annular ROI towards the apex was automatically measured during a cardiac cycle by the software. The displacement of the mid-portion of the mitral annulus was determined and indexed by LV length as TMAD. TMAD obtained from apical 4- and 2-chamber images was designated as $TMAD_{4ch}$ and $TMAD_{2ch}$, respectively, and their the mean value ($TMAD_{av}$) was calculated.

Data Reproducibility

Intra- and interobserver agreements in $TMAD_{4ch}$, $TMAD_{2ch}$, and GLS were evaluated by measuring these parameters in 10 randomly selected cases twice by the same observer or by 2 independent observers, respectively. Intraclass correlation coefficients (ICC) with 95% confidence intervals (CI) were calculated. As shown in **Table 1**, the measurement of all these parameters showed excellent intraobserver agreement. GLS also had excellent interobserver agreement, and $TMAD_{4ch}$ and $TMAD_{2ch}$ showed good interobserver agreement.

Statistical Analysis

Continuous variables are expressed as the median with interquartile range (IQR) and categorical variables are expressed as absolute frequencies or relative percentages. Comparisons were made using 1-way analysis of variance (ANOVA) for continuous variables, and the significance of differences was calculated using Tukey's honestly significant difference (HSD) test for factor analysis. Categorical variables were compared using Fisher's exact test. Correlation coefficients were compared using Z scores produced by Fisher's r to z transformation. To determine the ability of each echocardiographic parameter to predict all-cause mortality, a Cox proportional hazard model was constructed including age, sex, risk factors, and each parameter. Event-free survival was analyzed using the Kaplan-Meier method with the log-rank test for group comparisons. Cut-off values of indices used for the Kaplan-Meier analysis in all study patients were arbitrarily determined.

All statistical analyses were performed using R (R Foundation for Statistical Computing, Vienna, Austria) with the graphical user interface EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan).

Results

Patient Characteristics

Of the 290 patients enrolled in the present study, 43 were excluded because of incomplete echocardiography study (n=33), poor image quality (n=8), and arrhythmia (n=2). The final study group consisted of 246 patients (median age 62 years [IQR 54–71 years], 85.7% male). The clinical characteristics of the patients are presented in **Table 2**; 171 (69.5%) patients had a history of hypertension, 190 (77.2%) had dyslipidemia, 96 (39.0%) had diabetes, 40 (16.3%) had prior MI, and 155 (63.0%) were smokers. Emergency coronary angiography was performed in all patients, and primary PCI was performed in 242 (98.4%). Anterior MI was observed in 82 (33.3%) patients, and 215 (87.3%) patients showed STEMI. Median CK and CK-MB concentrations were 2,038 IU/L (IQR 938–4,045 IU/L) and 136 IU/L (IQR 67–269 IU/L), respectively. Peak CK ≥5,000 IU/L was observed in 43 (17.5%) patients, whereas 66 (26.8%) patients had CK ≤1,000 IU/L.

Measurement of GLS and TMAD

Figure 1 shows representative images in 2 patients with inferior wall MI. In Case A (57 years old, male), peak longitudinal strain was well preserved in each LV segment 2 weeks after MI (**Figure 1**, **Upper left**) and GLS was calculated to be 19.5%. $TMAD_{4ch}$ was calculated to be 12.2% (**Figure 1**, **Upper right**) and LVEF was measured as 63%. In Case B (39 years old, male), peak longitudinal strain was widely impaired within the inferior lesion, and GLS was reduced to 12.2% (**Figure 1**, **Lower left**). $TMAD_{4ch}$ was reduced to 9.6% (**Figure 1**, **Lower right**) and LVEF was 44.5%.

$TMAD_{4ch}$ and $TMAD_{2ch}$ were successfully measured in 240 (97.5%) and 210 (85.3%) patients, respectively, within 2 min. The main reason for unsuccessful TMAD measurement was drift of the apical ROI during a cardiac cycle.

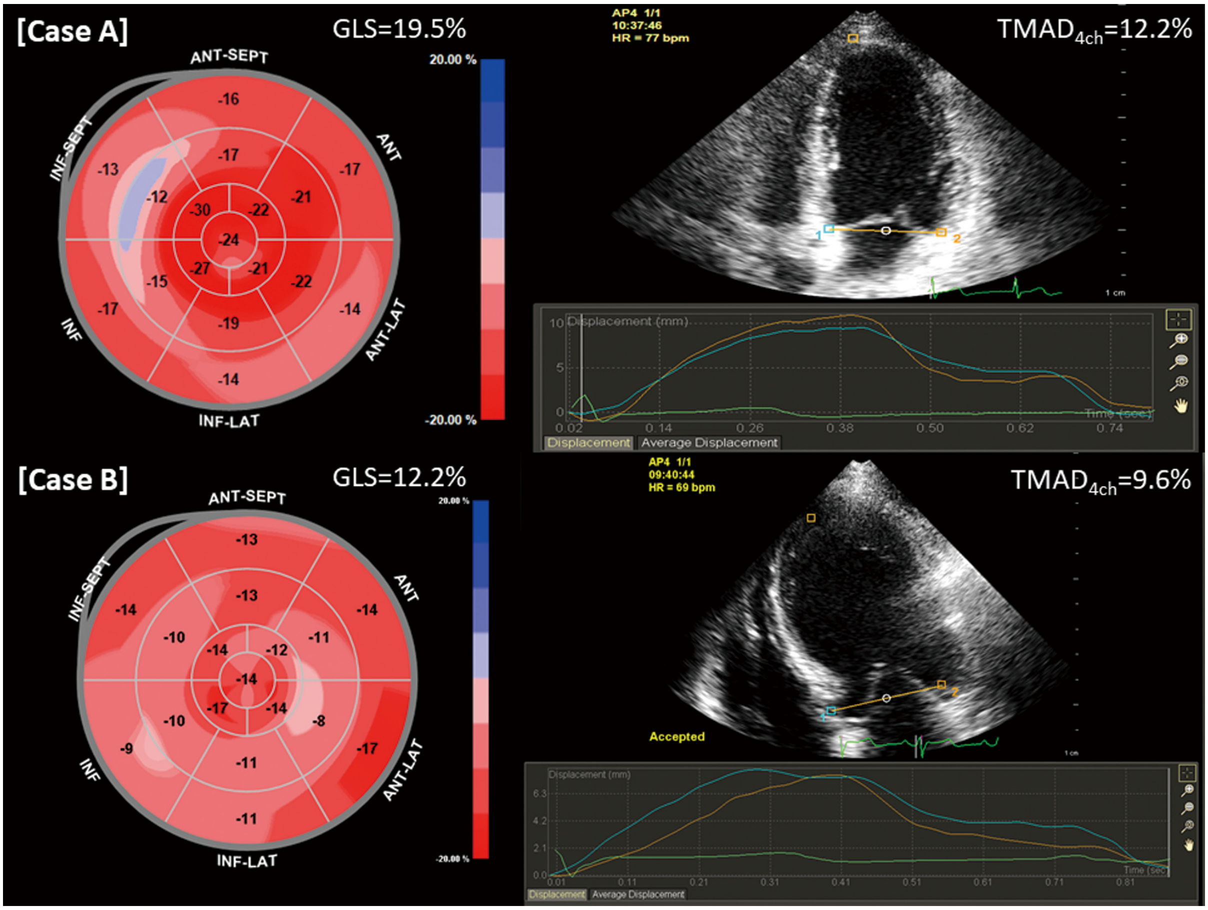

Figure 1. Representative images in patients with inferior myocardial infarction (MI). Longitudinal strain and tissue mitral annular displacement measured from apical 4-chamber views ($TMAD_{4ch}$) from 2 patients with inferior MI. (**Left**) Segmental peak longitudinal strain values are shown on a bull's eye plot. (**Right**) The movement of regions of interest (ROIs) on both sides of the mitral annulus towards the apex during systole was traced, and the movement of the midpoint of annular ROIs was indexed by left ventricle (LV) length to calculate TMAD. In Case A, global longitudinal strain (GLS) was 19.5% and $TMAD_{4ch}$ was 12.2%; in Case B, reductions were seen in both GLS (12.2%) and $TMAD_{4ch}$ (9.6%). ANT, anterior; INF, inferior; LAT, lateral; SEPT, septum.

GLS was correctly measured in 214 (87.0%) patients. The major reason for unsuccessful GLS measurement was inappropriate image quality for proper speckle tracking in some of the LV segments. A significant difference was observed in the rate of successful measurement among the 3 indices (P<0.0001). Median values for $TMAD_{4ch}$, $TMAD_{2ch}$, and $TMAD_{av}$ in the study group were 12.6% (IQR 10.1–14.9%), 12.4% (IQR 10.0–14.6%), and 12.7% (IQR 10.7–14.6%), respectively. GLS was 17.4% (IQR 14.2–19.2%) and LVEF was 55.3% (IQR 49.8–60.8%).

There were significant correlations among TMAD parameters; R=0.72 (95% CI 0.65–0.78) between $TMAD_{4ch}$ and $TMAD_{2ch}$, R=0.93 (95% CI 0.91–0.95) between $TMAD_{4ch}$ and $TMAD_{av}$, and R=0.92 (95% CI 0.90–0.94) between $TMAD_{2ch}$ and $TMAD_{av}$ (**Figure 2**, **Upper panels**). TMAD parameters were significantly correlated with GLS (R=0.71; 95% CI 0.63–0.76), and there were correlations between $TMAD_{4ch}$ and GLS (R=0.71; 95% CI 0.64–0.77), $TMAD_{2ch}$ and GLS (R=0.75; 95% CI 0.69–0.81), and $TMAD_{av}$ and GLS (**Figure 2**, **Middle panels**). There were no significant differences in the correlation coefficients between GLS and TMAD parameters. All these correlations were statistically significant (P<0.0001). Although the correlation coefficient between $TMAD_{av}$ and GLS tended to be better in 81 patients with impaired GLS (<16%; R=0.66) than in 129 patients with preserved GLS (≥16%; R=0.48), the difference did not reach statistical difference (P=0.052).

Because TMAD parameters may be differently affected by the location of the MI, we investigated its effects on correlations between TMAD parameters and GLS. Both $TMAD_{4ch}$ and GLS were reliably measured in 213 patients, and there was no difference in correlation coefficients between 69 patients (32.4%) with anterior wall MI (R=0.72) and those with inferior/posterior MI (R=0.66; P=0.38). $TMAD_{2ch}$ and GLS were also measured in 210 patients, and there was no difference in the correlation coefficients between the 2 groups (anterior wall MI [n=66], R=0.74; inferior/posterior MI [n=144], R=0.67; P=0.36). There was also no difference in the correlation coefficients for $TMAD_{av}$ and GLS between the anterior wall MI (n=66; R=0.77) and inferior/posterior MI (n=144; R=0.73) groups (P=0.56).

TMAD parameters were also moderately correlated

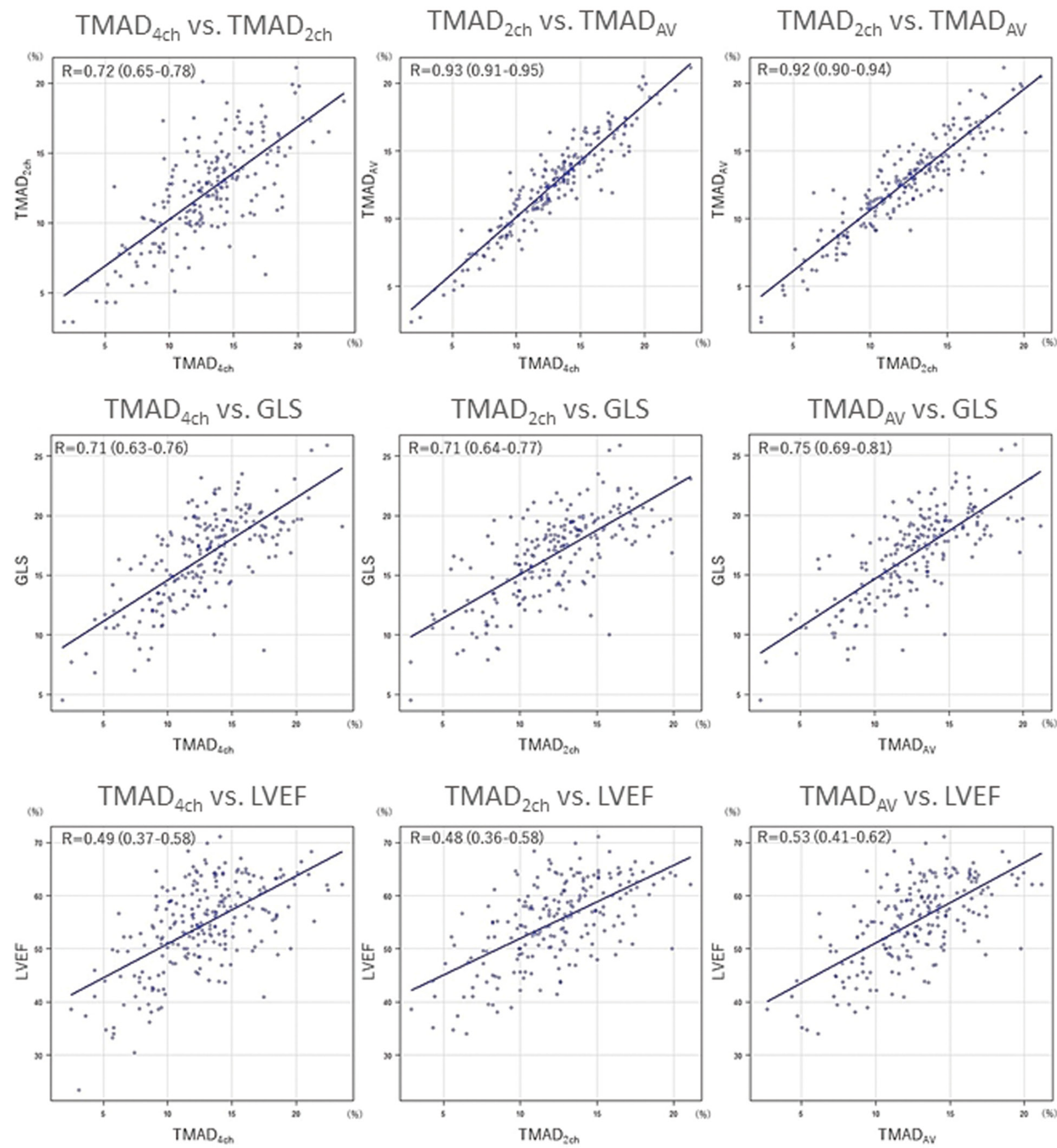

Figure 2. Correlations among tissue mitral annular displacement (TMAD) and other echocardiographic parameters. (**Upper**) There were good correlations among TMAD parameters (TMAD measured apical 4- and 2-chamber views [$TMAD_{4ch}$ and $TMAD_{2ch}$, respectively], mean TMAD [$TMAD_{av}$]). All TMAD parameters showed good correlations with global longitudinal strain (GLS; **Middle**) and moderate correlations with left ventricular ejection fraction (LVEF; **Lower**). R values are given on each plot, with 95% confidence intervals in parentheses.

Table 3. Correlation Between Echocardiography and Enzyme Parameters

	Peak CK		Peak CK-MB	
	R (95% CI)	P value	R (95% CI)	P value
$TMAD_{4ch}$	0.20 (0.07, −0.31)	0.002	0.21 (0.09, 0.33)	0.001
$TMAD_{2ch}$	0.20 (0.07, 0.33)	0.003	0.25 (0.12, 0.37)	0.0003
$TMAD_{av}$	0.20 (−0.06, 0.33)	0.004	0.24 (0.10, 0.36)	0.0006
GLS	0.26 (0.12, 0.37)	0.0002	0.26 (0.13, 0.38)	0.0001
LVEF	0.18 (0.05, 0.30)	0.006	0.24 (0.12, 0.36)	0.0002

LVEF, left ventricular ejection fraction; $TMAD_{av}$, mean value of $TMAD_{4ch}$ and $TMAD_{2ch}$. Other abbreviations as in Tables 1,2.

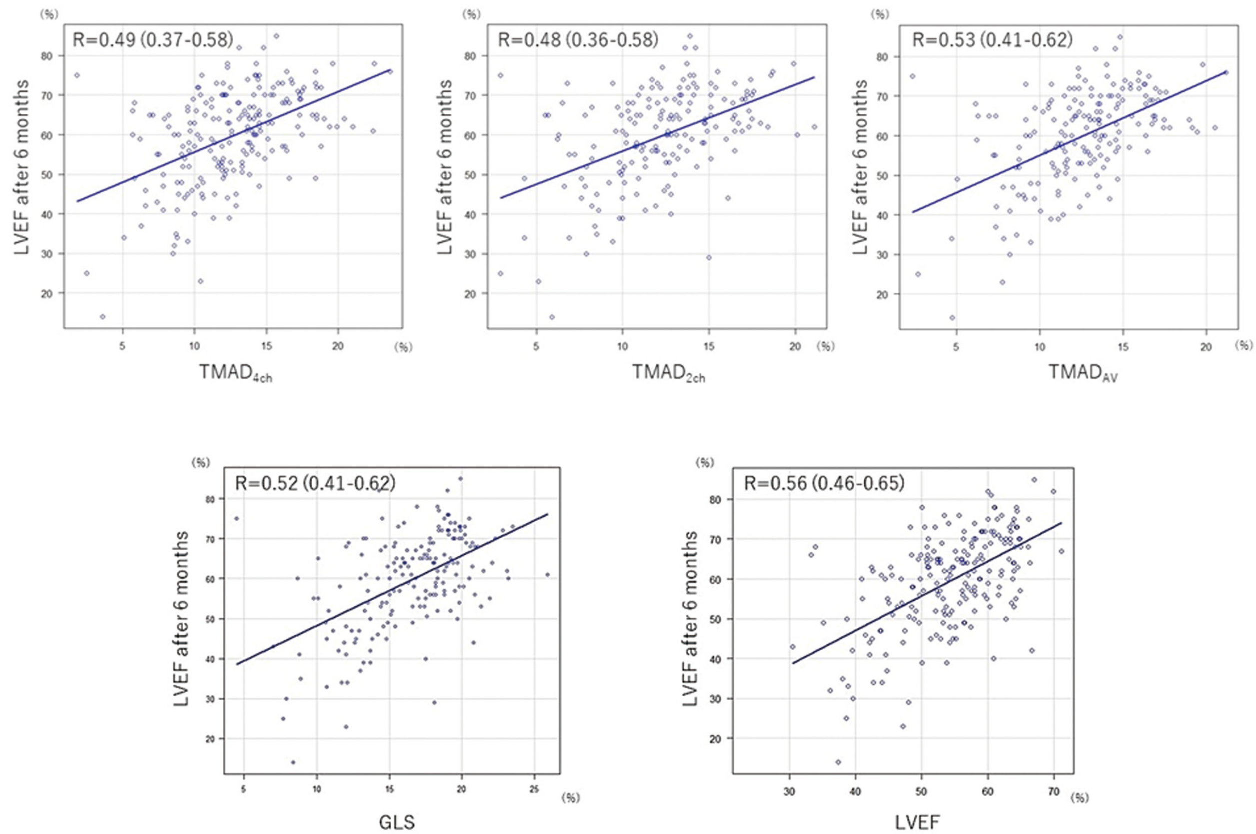

Figure 3. Correlations among echocardiographic parameters and left ventricular ejection fraction (LVEF) at 6 months after myocardial infarction. (**Upper**) There were significant correlations between LVEF at 6 months and all tissue mitral annular displacement (TMAD) parameters. There were also significant correlations between LVEF at 6 months and global longitudinal strain (GLS; **Lower left**) and LVEF at 2 weeks (**Lower right**). R values are given on each plot, with 95% confidence intervals in parentheses.

Table 4. Cox Proportional Hazard Models for Prediction of All-Cause Death

	Coefficient	Hazard ratio	95% CI		P value
			Upper	Lower	
Model 1 including $TMAD_{av}$					
Age	0.072	1.074	0.960	1.202	0.21
Male sex	1.699	5.468	0.338	88.460	0.23
Diabetes	−1.407	0.245	0.021	2,823	0.26
Hypertension	0.178	0.00006	0.000000	–	1.0
Dyslipidemia	0.672	1.957	0.266	14,400	0.51
Anterior MI	−0.185	0.0000009	0.00000	–	1.0
$TMAD_{av}$	−0.297	0.743	0.565	0.977	0.033
Model 2 including GLS					
Age	0.075	1.078	0.964	1.206	0.19
Male sex	2.016	7.508	0.458	123.200	0.16
Diabetes	−1.525	0.218	0.018	2.582	0.23
Hypertension	0.179	0.00006	0.000000	–	1.0
Dyslipidemia	0.621	1.861	0.244	14,170	0.55
Anterior MI	−0.183	0.0000001	0.00000	–	1.0
GLS	0.260	1.297	1.028	1.638	0.029

CI, confidence interval; GLS, global longitudinal strain; MI, myocardial infarction; $TMAD_{av}$, mean value of tissue mitral annular displacement measured on images from apical 4- and 2-chamber views.

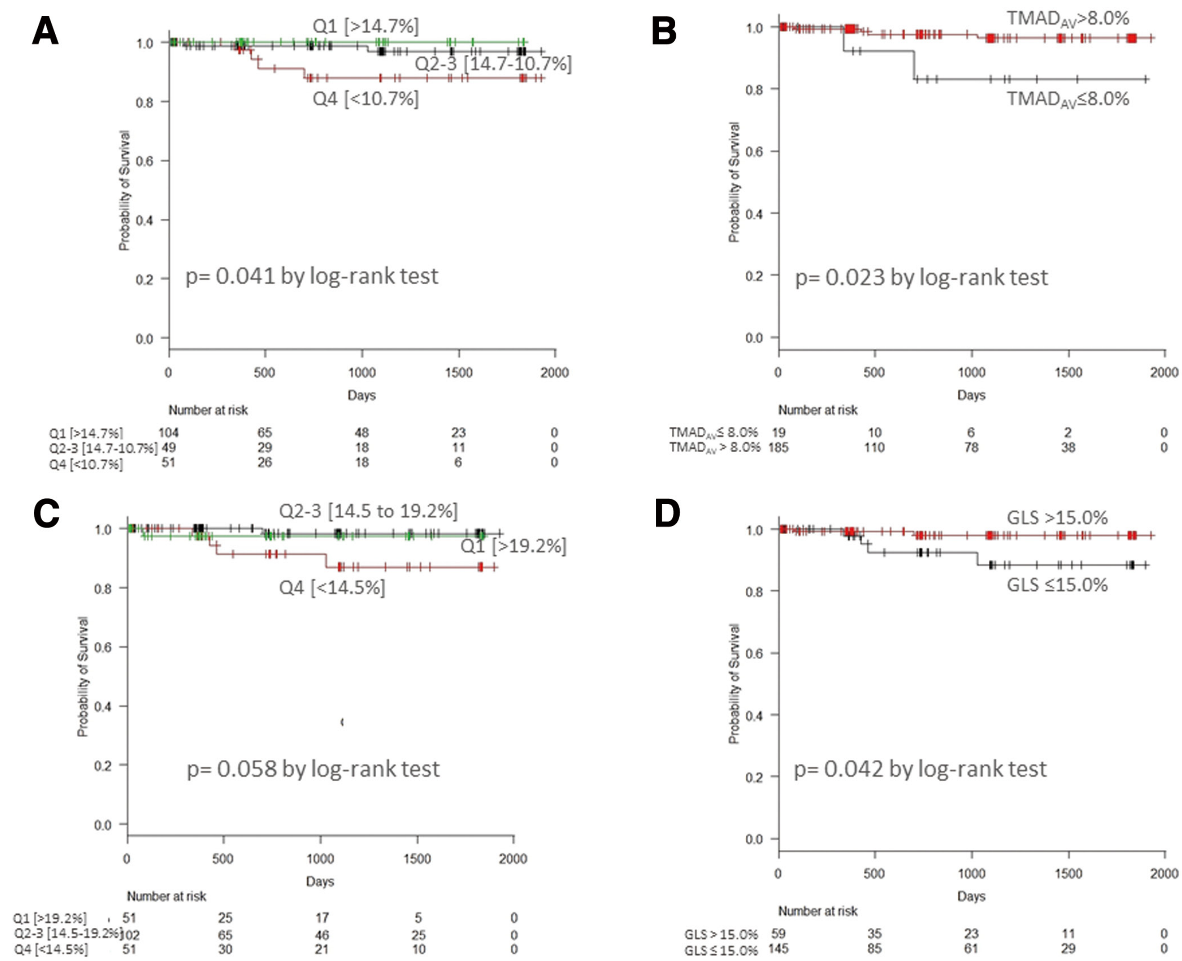

Figure 4. Kaplan-Meier curves for all-cause death in patients with myocardial infarction. All-cause mortality during the follow-up period (median 735 days) was analyzed among 204 patients in whom global longitudinal strain (GLS) and tissue mitral annular displacement from apical 4- and 2-chamber views ($TMAD_{4ch}$ and $TMAD_{2ch}$, respectively) were all measured. (**A**) Kaplan-Meier curves among patients divided according to quartiles of mean TMAD ($TMAD_{av}$): upper 25% (Q1; >14.7%), middle range (Q2–3; 10.7–14.7%), and lower 25% (Q4; <10.7%). Patients in Q1 had higher mortality than those in the other groups (P=0.041, log-rank test). (**B**) Kaplan-Meier curves among patients divided into 2 groups based on $TMAD_{av}$. Mortality was higher for patients with $TMAD_{av}$ ≤8.0% than >8.0% (P=0.023). (**C**) Dividing patients into groups based on the interquartile range of GLS (Q1 [>19.2%], Q2–3 [14.5 to 19.2%], and Q4 [<14.5%]) revealed no significantly associations with mortality (P=0.058). (**D**) GLS was associated with all-cause mortality when patients were divided into 2 groups using 15.0% as a cut-off value.

(P<0.0001) with LVEF (R=0.49; 95% CI 0.37–0.58), and there were correlations between $TMAD_{4ch}$ and LVEF (R=0.48; 95% CI 0.36–0.58), $TMAD_{2ch}$ and LVEF (R=0.53; 95% CI 0.41–0.62), and $TMAD_{av}$ and LVEF (**Figure 2**, **Lower panels**). The correlation between each TMAD parameter and GLS was better than that between TMAD and LVEF ($TMAD_{4ch}$, P=0.004; $TMAD_{2ch}$, P=0.004; $TMAD_{av}$, P=0.002). There was a good correlation between GLS and LVEF (R=0.75; 95% CI 0.69–0.81; P<0.0001).

Association Between Echocardiographic Indices and Peak CK/CK-MB and Functional Outcomes

We investigated the correlation between echocardiographic indices and peak CK and CK-MB. As indicated in **Table 3**, there were weak but significant correlations between TMAD parameters and peak CK and CK-MB values. GLS and LVEF were also weakly correlated with peak CK and CK-MB values (**Table 3**).

Figure 3 shows the relationship between LVEF at 6 months and echocardiographic indices at baseline. There were significant correlations between LVEF at 6 months and $TMAD_{4ch}$ (R=0.49; 95% CI 0.37–0.58), $TMAD_{2ch}$ (R=0.48; 95% CI 0.36–0.58), and $TMAD_{av}$ (R=0.53; 95% CI 0.41–0.62). LVEF at 6 months was also correlated with GLS (R=0.52; 95% CI 0.41–0.62) and baseline LVEF (R=0.56; 95% CI 0.46–0.65). All these correlations were statistically significant (P<0.0001). There was no difference in the correlation coefficients between GLS and LVEF at 6 months and between $TMAD_{av}$ and LVEF (P=1.00).

Echocardiographic Indices and Mortality After MI

To compare the predictive value of TMAD parameters with that of GLS for all-cause mortality, we selected 204 patients in whom GLS, $TMAD_{4ch}$, and $TMAD_{2ch}$ were all successfully measured. Age (median 62 years [IQR 54–71 years]), sex (86.3% male), and other clinical parameters did not differ significantly between the 204 selected patients and the original study cohort. The 204 selected patients were followed-up for median of 735 days (IQR 358–1,346 days), and 6 patients (2.9%) died during the follow-up period (their characteristics are summarized in **Supplementary Table 1**). Cox hazard proportional model analysis for each parameter indicated that GLS (P=0.029; hazard ratio [HR] per unit 1.30; 95% CI 1.03–1.64) or $TMAD_{av}$ (P=0.033; HR per unit 0.74; 95% CI 0.57–0.98) were significant predictors for all-cause mortality (**Table 4**). LVEF (P=0.11), $TMAD_{4ch}$ (P=0.08), and $TMAD_{2ch}$ (P=0.059) were not selected as independent predictors of all-cause mortality.

Patients were divided into 3 groups based on the IQR of $TMAD_{av}$: the upper 25% (Q1; >14.7%), middle range (Q2–3; 10.7–14.7%), and lower 25% (Q4; <10.7%). Kaplan-Maier curves showed the patients with the lowest $TMAD_{av}$ had higher mortality during the follow-up period than the other groups (P=0.041, log-rank test; **Figure 4A**). There were no differences in clinical background among the groups, except for age and peak CK/CK-MB (**Supplementary Table 2**). A similar analysis based on the IQR of GLS (i.e., Q1, >19.2%; Q2–3, 14.5–19.2%; and Q4, <14.5%) revealed no significant associations with mortality (P=0.058, **Figure 4C**). Conversely, patients with GLS ≤15.0% had higher mortality than those with GLS >15.0% (P=0.042; **Figure 4D**). In addition, mortality was higher among patients with $TMAD_{av}$ ≤8.0% than >8.0% (P=0.023; **Figure 4B**).

Discussion

In the present study, we measured TMAD and GLS in 246 consecutive patients 2 weeks after MI. All TMAD parameters ($TMAD_{4ch}$, $TMAD_{2ch}$, and $TMAD_{av}$) showed good correlation with GLS. TMAD parameters and GLS were significantly correlated with LVEF. All these echocardiographic indices were significantly correlated with peak CK and CK-MB values, as well as with LVEF measured 6 months later. GLS and $TMAD_{av}$ were associated with all-cause mortality during the follow-up period (median 1,242 days). Kaplan-Meier curve analysis demonstrated that $TMAD_{av}$ significantly discriminated patients with higher all-cause mortality when patients were divided into 3 groups into the upper 25% (>14.7%), middle range (10.7–14.7%), and lower 25% (<10.7%) of $TMAD_{av}$ (P=0.041, log-rank test). In addition, mortality was higher in patients with GLS ≤15.0% than >15.0% (P=0.042). These results indicate the possibility of using TMAD as an alternative index to GLS in patients with MI.

TMAD and GLS in Patients With MI

Although TMAD can be interpreted as the volume change during systole and it was correlated with LVEF, its correlation with GLS was significantly better than with LVEF. The LV wall has complex myocardial fiber orientation with longitudinal and circumferential fibers showing a continuous variation in angulations. TMAD and GLS represent the shortening of longitudinal fibers, whereas LVEF reflects all the radial, circumferential, and longitudinal contractions. Thus, TMAD and GLS, representative of LV longitudinal deformity, could have different clinical implications from LVEF.

Infarct size is a major determinant of functional and clinical outcomes after MI.[30,31] Although the present study demonstrated that TMAD parameters and GLS were significantly correlated with peak CK/CK-MB values, their correlation with CK/CK-MB was only modest (**Table 3**). The correlation of LVEF with CK/CK-MB was no better than that of TMAD or GLS with CK/CK-MB. However, these echocardiographic indices were well correlated with LVEF after 6 months (TMAD parameters, R=0.48–0.53, GLS, R=0.52; LVEF at 2 weeks, R=0.56). CK and CK-MB are surrogate markers of infarct size and have only a weak relationship with infarct size determined by ^{18}F-fluorodeoxyglucose positron emission tomography[32] or by cardiac magnetic resonance imaging (CMR).[33] GLS is reported to be correlated with infarct size measured by CMR.[9,11] TMAD may represent infarct size better than CK/CK-MB and GLS.

The present study had a limited number of patients, and these patients only had modest infarct size and very low mortality, which made it difficult to construct a Cox hazard model including all the echocardiographic parameters and to determine cut-off values using proper statistical methods instead of assigning arbitrary values. Moreover, the number of deaths during the follow-up period was too small to exclude the possibility that the results regarding all-cause death may be just coincidental. Thus, the present results may be inconclusive about the prognostic value of $TMAD_{av}$ and GLS. This may also explain why LVEF was not associated with mortality, in contrast with findings in prior studies.[1,2]

In the presence of asynergy segments, movement of the mitral annulus may be observed differently on each image plane, and TMAD parameters may be affected by the location of the infarct area. $TMAD_{4ch}$ and $TMAD_{2ch}$ showed excellent correlation in the present study, and both showed similar correlations with GLS. They also showed similar correlations with CK/CK-MB and LVEF at 6 months, and the correlations were not better for $TMAD_{av}$. One of the advantages of TMAD is that it can be obtained from a single image plane. $TMAD_{av}$ may have better ability to predict all-cause mortality than $TMAD_{4ch}$ and $TMAD_{2ch}$, but it may reduce this advantage. The other advantage of TMAD is that it is less dependent on image quality than GLS. GLS could not be measured in 13% of patients in the present study, mostly because of insufficient image quality in some myocardial segments, whereas $TMAD_{4ch}$ was correctly measured in almost all patients (97.5%). $TMAD_{2ch}$ was assessed in only 85.3% of patients. The lateral part of the mitral annulus may be hard to visualize from an apical 2-chamber view in some patients. $TMAD_{4ch}$ may be the most suitable of the TMAD parameters for clinical practice, whereas $TMAD_{2ch}$ and $TMAD_{av}$ should be used based on the purpose of their assessment and depending on the conditions of patients.

TMAD also has some limitations compared with GLS. TMAD does not assess segmental deformation as strain analysis by 2DSTE. TMAD may be affected by some conditions that do not affect GLS, including LV curvature, right ventricle dysfunction, mitral valve disease, and mitral ring calcification. In the presence of pericardial effusion, TMAD may be incorrect because of a mobile apex. Even though strain measurement by 2DSTE is somehow vendor dependent, the vender-independent normal range of GLS is determined as 20±2%.[7] TMAD is measured only by machines from a single vendor (Philips), and its normal range has still not been determined.

Study Limitations

The present study was conducted as a single-center retrospective study with a limited number of patients; therefore, the results must be interpreted carefully. Many patients had only a small infarct size and good prognosis, which may have resulted in an underestimation of the prognostic value of echocardiographic indices. As a multicenter registration study, the OACIS collected only mortality as prognostic data. We could not analyze the association between echocardiographic parameters and other major cardiovascular events, such as MI, heart failure hospitalization, and stroke. We only evaluated all-cause mortality in the present study, with the cause of death not specified, and the prognostic value for cardiovascular death or events was not investigated. It should be noted that the present study could not determine superiority between TMAD and GLS with regard to prognostic value. Even though GLS and TMAD could be successfully measured in most patients, $TMAD_{2av}$ and GLS could not be obtained in approximately 15% of study subjects. We only selected patients in whom all of GLS, $TMAD_{4ch}$, and $TMAD_{2ch}$ were obtained for the analysis of mortality, which excluded 17% of potential study patients. Even though this is not large proportion, the exclusions may have affected the results of the present study somehow.

Despite these limitations, the findings of the present study suggest that TMAD has the potential to be an easy and less image-dependent alternative modality to GLS for risk stratification of patients with MI. Unfortunately, TMAD is less frequently used than GLS. To make this useful modality more widely used in clinical situations, a prospective multicenter study should be performed to evaluate the feasibility and potential of TMAD.

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IRB Information

This study was approved by the Ethics Committee of Sakurabashi Watanabe Hospital (Reference no. 17-32).

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Supplementary Files

Please find supplementary file(s);
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