Original Article

Check for updates

Three-Dimensional Myocardial Strain for the Prediction of Clinical Events in Patients With ST-Segment Elevation Myocardial Infarction

Wonsuk Choi, MD[1,*], Chi-Hoon Kim, MD[2,*], In-Chang Hwang (iD), MD[1],
Chang-Hwan Yoon (iD), MD, PhD[1], Hong-Mi Choi (iD), MD[1], Yeonyee E Yoon (iD), MD, PhD[1],
In-Ho Chae (iD), MD, PhD[1], and Goo-Yeong Cho (iD), MD, PhD[1]

[1]Division of Cardiology, Department of Internal Medicine, Seoul National University College of Medicine and Cardiovascular Center, Seoul National University Bundang Hospital, Seongnam, Korea
[2]Cardiovascular Center, Sejong General Hospital, Bucheon, Korea

OPEN ACCESS

Address for Correspondence:
Goo-Yeong Cho, MD, PhD
Division of Cardiology, Department of Internal Medicine, Seoul National University College of Medicine and Cardiovascular Center, Seoul National University Bundang Hospital, 82 Gumi-ro 173beon-gil, Bundang-gu, Seongnam 13620, Korea.
Email: cardioch@snu.ac.kr

*Wonsuk Choi and Chi-Hoon Kim contributed equally to this work.

ORCID iDs
In-Chang Hwang (iD)
https://orcid.org/0000-0003-4966-3924
Chang-Hwan Yoon (iD)
https://orcid.org/0000-0001-6305-4442
Hong-Mi Choi (iD)
https://orcid.org/0000-0002-6856-2486
Yeonyee E Yoon (iD)
https://orcid.org/0000-0002-8479-9889

ABSTRACT

BACKGROUND: Two-dimensional (2D) strain provides more predictive power than ejection fraction (EF) in patients with ST-elevation myocardial infarction (STEMI). 3D strain and EF are also expected to have better clinical usefulness and overcome several inherent limitations of 2D strain. We aimed to clarify the prognostic significance of 3D strain analysis in patients with STEMI.

METHODS: Patients who underwent successful revascularization for STEMI were retrospectively recruited. In addition to conventional parameters, 3D EF, global longitudinal strain (GLS), global area strain (GAS), as well as 2D GLS were obtained. We constructed a composite outcome consisting of all-cause death or re-hospitalization for acute heart failure or ventricular arrhythmia.

RESULTS: Of 632 STEMI patients, 545 patients (86.2%) had a reliable 3D strain analysis. During median follow-up of 49.5 months, 55 (10.1%) patients experienced the adverse outcome. Left ventricle EF, 2D GLS, 3D EF, 3D GLS, and 3D GAS were significantly associated with poor outcomes. (all, p < 0.001) The maximum likelihood-ratio test was performed to evaluate the additional prognostic value of 2D GLS or 3D GLS over the prognostic model consisting of clinical characteristics and EF, and the likelihood ratio was 15.9 for 2D GLS (p < 0.001) and 1.49 for 3D GLS (p = 0.22).

CONCLUSIONS: The predictive power of 3D strain was slightly lower than the 2D strain. Although we can obtain 3D strains, volume, and EF simultaneously in same cycle, the clinical implications of 3D strains in STEMI need to be investigated further.

Keywords: ST elevation myocardial infarction; Prognosis; Echocardiography, three-dimensional

INTRODUCTION

With advances in technology that combine information from myocardial deformation imaging and conventional echocardiography, patients with cardiovascular disease can be evaluated in a more multi-layered fashion. Assessment of ischemic heart disease using myocardial strain analysis is an excellent example of this approach. If a two-dimensional

In-Ho Chae (iD)
https://orcid.org/0000-0003-1644-2105
Goo-Yeong Cho (iD)
https://orcid.org/0000-0002-7067-5535

Conflict of Interest
The authors have no financial conflicts of interest.

Author Contributions
Data curation: Hwang IC, Yoon CH, Choi HM, Yoon YE, Chae IH, Cho GY; Formal analysis: Choi W, Kim CH, Hwang IC, Yoon CH, Choi HM, Yoon YE, Cho GY; Investigation: Cho GY; Methodology: Hwang IC, Yoon YE, Chae IH, Cho GY; Writing - original draft: Choi W, Kim CH, Cho GY; Writing - review & editing: Choi W, Cho GY.

(2D) myocardial strain index such as global longitudinal strain (GLS) can be obtained using speckle tracking and other post-processing techniques, the patient's actual infarct size can be accurately assessed while maintaining appropriate temporal resolution.[1] Moreover, myocardial strain is not only useful in evaluating myocardial viability and predicting future ventricular remodeling,[2,3] but also in assessing the prognosis. Patients with higher end-systolic GLS values are at a greater risk for major clinical events, such as cardiac death or re-hospitalization due to heart failure.[4-6] This association persists even after adjusting for other significant risks factors.[7-9]

However, 2D strain imaging has some inherent limitations. Strain information obtained from different image sections must be integrated in order to calculate the global strain value of the entire left ventricle (LV).[1] Therefore, it is impossible to assess the global strain using the images obtained in the same cardiac cycle, and it takes a relatively long time to measure the strain value. In addition, the three-dimensional (3D) motion of the myocardium is analyzed on a 2D plane, the so-called 'out-of-plane' phenomenon occurs. Because the target segment does not remain in the same cross-sectional plane during a given cardiac cycle, this is particularly prominent when processing circumferential or radial strain using short-axis images.[10]

3D echocardiography is considered to be overcome these shortcomings. As the 3D volumetric data of the entire ventricle can be obtained with a multiarray transducer, 3D strain analysis has begun to be applied in the field of clinical echocardiography. Many manufacturers provide semi-automated tools to easily apply 3D imaging. Although we could obtain various 3D strains, LV mass, LV volume and ejection fraction (EF) simultaneously, the use of 3D strains have some inherent drawbacks. Compared with 2D strain imaging, 3D strains imaging has relatively low sampling rate and spatial resolution, and the standardization of the image processing algorithms has not yet been established.[10-12] Furthermore, data are needed to verify the prognostic power of 3D strains analysis. To date, no large-scale study has demonstrated the use of a 3D strain indices as an effective prognostic indicator.

Based on these points, we aimed to clarify the prognostic significance of 3D strain analysis, especially in those patients with ST-segment elevation myocardial infarction (STEMI) who are most likely to benefit from 3D strain analysis.

METHODS

Patient population and revascularization
For this study, patients who underwent successful revascularization for STEMI at the Seoul National University Bundang Hospital, from June 2011 to April 2017 were retrospectively recruited. The revascularization mode included primary percutaneous coronary intervention (PCI) or thrombolysis with no limitations as to procedural details. However, only patients who met the criteria stipulated by the current guidelines were included.[13] Patients who did not have a sinus rhythm or those who had cardiogenic shock requiring mechanical support or had a mechanical ventilator for more than 24 hours were excluded from the study in order to achieve proper 3D image analyses. Patients who died during the index hospitalization were also excluded from the analysis. This study was approved by the Institutional Review Board (IRB) of Seoul National University Bundang Hospital and involved all necessary procedures for approval (IRB No. B-1607-353-104). The researchers were exempted from the requirement

to obtain consent from individual patients provided that the study did not include the patients' personal information.

Echocardiographic evaluation and strain analysis

Since June 2011, 3D echocardiography has been systematically performed in all patients who are admitted with acute myocardial infarction at the Seoul National University Bundang Hospital. All the images were stored in a dedicated network attached storage, and the results have been used for patient evaluation. In this study, the echocardiographic images used for the 3D analysis were limited to those obtained within two days after revascularization during the index hospitalization. 3D echocardiograms were obtained using a dedicated transthoracic transducer (4V-D) with a matrix phased-array and a standalone station such as Vivid E9 (GE Vingmed Ultrasound of the GE Healthcare, Horten, Norway) by following the latest recommendations.[14] Subsequently, the 3D strain indies were obtained by post-processing in a separate workstation (EchoPAC Software Workstation, V201) equipped with a 4D Auto LVQ system. To secure the optimal image quality for 3D strain analysis, we set the volume rate at about 30–50 times per second (more than 40% of the patient's heart rate) and adjusted the sector width and depth as well as the gain so that the entire left ventricle could be presented within the scan range. Scanning was performed during a few cardiac cycles to obtain adequate 3D volume data, and patients were instructed to hold their breath for several seconds to minimize stitching artifacts. Standardized routine 2D echocardiography was simultaneously conducted on all patients in the same session.

Image analysis and strain measurements were performed by a number of skilled and independent sonographers. For 3D analysis, the apical window 3D image was aligned as closely as possible to the long axis of the LV, and the positions of the mitral annulus and apex were determined in order to establish the endocardial border. After contouring the end-diastolic frame, the end-diastolic and end-systolic LV volume, LV mass, and 3D LV EF were automatically calculated if the extracted LV boundary was observed to correspond well to the actual image. Unless the image quality was poor such that three or more myocardial segments were not suitable for analysis, tracking of the 3D region of interest was conducted throughout the cardiac cycle. Then, the strain analysis of 16 standardized segments was automatically performed. For each frame of a cardiac cycle, the global strain value, which is the mean value of the segmental strain values weighted with the initial area of the myocardial segments, was calculated. Finally, we obtained the following four global strain indices in order to evaluate global LV function from the instantaneous strain values of the end-systole: the global strain value of the area strain (global area strain; GAS), as well as the GLS, global circumferential strain (GCS), and global radial strain (GRS). In addition to the 3D strain, 2D GLS and conventional echocardiographic parameters were also assessed. Using the images of the three apical views, 2D GLS was calculated as the average value of the peak systolic longitudinal strain values of 16 myocardial segments.

Follow-up and composite outcome

Data collection pertaining to the patients' clinical outcomes, including basic demographic information and procedural details at the time of admission, was handled by independent and well-trained research personnel. The clinical course of each patient was followed up for a maximum of 8 years. All clinical events were collected using a database of the National Statistical Office and patients' electrical medical records. In cases where the progress was unclear or if it was judged to be missing from the follow-up, mortality data from Statistics Korea, the Korean National Statistics Office, were used to enhance the reliability of the

data. To evaluate the clinical outcomes, we constructed a composite outcome consisting of all-cause death or re-hospitalization due to acute decompensation of heart failure (ADHF) or ventricular arrhythmia. The adjudication criteria for the clinical events were the same as those prescribed in the latest guideline.[15]

Statistical analysis

In the case of continuous variables, the results were summarized using mean and standard deviation, and discrete variables were expressed using percentages. The averages were compared using the appropriate tests such as the Student's t-test, and the ratios were compared using the χ^2 test or the Fisher's exact test. Continuous data were tested for normal distribution using the Kolmogorov-Smirnov test. N-terminal pro b-type natriuretic peptide (NT-proBNP) levels, high-sensitivity C-reactive protein (hs-CRP), creatine kinase-myocardial band (CK-MB), and troponin I were non-normally distributed and were analyzed using the nonparametric Kruskal-Wallis test.

To evaluate the statistical power of the echocardiographic parameters, the receiver operating characteristic (ROC) analyses were conducted. In addition to 2D EF, 2D regional wall motion index and 2D GLS, 3D EF, 3D LV mass index, 3D GLS, 3D GAS, 3D GCS, and 3D GRS were each selected as marker values for the ROC curves. All strain values are expressed as absolute value. To find cut-off values for each echo parameters, we constructed Cox proportional hazards regression model with sex, age, body mass index (BMI), underlying disease including hypertension, diabetes mellitus, dyslipidemia, history of CVA, previous myocardial infarction, presence of QRS duration over 120 milli-seconds on initial electrocardiogram, serum creatinine, and each echo parameters. The values that maximize the C-index of the model at the end of follow-up were set to the cut-off values. Then the hazard ratios (HRs) and 95% confidence intervals of the HR at the predetermined cut-off values were calculated. The Kaplan-Meier method was used to demonstrate the occurrence of composite outcome between the 2 groups divided by the cut-off values.

To evaluate additional prognostic importance of strain indices over conventional risk factors, the maximum likelihood ratio tests were conducted. First, we compared basic model which only included conventional clinical and laboratory risk factors of adverse outcome on coronary artery disease with a model that consists of basic risk factors and each echocardiographic parameter such as 2D LV EF, 2D GLS or 3D GLS. Then we set another model consisting of conventional risk factors and LV EF combined, figured out whether the 2D or 3D strain indices could provide additional predictive and power to the model. The likelihood ratios and p-values were calculated to evaluate the predictive power of the strain indices. The results were obtained using statistical packages such as R and SPSS (version 22; IBM SPSS, Chicago, IL, USA). When the significance was less than 0.05, the 2-sided analysis results were considered statistically significant.

Reproducibility of 2D and 3D strain

Variability in the measurement of 2D and 3D strain was evaluated in 20 randomly selected patients. For intra-observer variability, the same observer re-measured the strain after 60 days for each selected patient. The interclass correlation coefficient of intra-observer variability for 3D GAS, 3D GLS, 3D LV EF and 2D GLS were 0.98, 0.96, 0.98 and 0.96 respectively. For the inter-observer variability, a second independent observer repeated the same analysis. The interclass correlation coefficient of inter-observer variability for 3D GAS, 3D GLS, 3D LV EF and 2D GLS were 0.97, 0.95, 0.90 and 0.94 respectively.

RESULTS

From June 2011 to April 2017, 632 patients met the selection criteria. Of these patients, 545 patients (86.2%) had optimal 3D echocardiograms to enable accurate strain analysis. Many of the remaining patients (86 cases) with suboptimal images had an arrhythmia or relatively large LV chamber or poor echo window, such that the entire LV structure within the 3D sample volume was unable to be adequately captured. In these patients, the global strain was difficult to obtain because the LV apex or other LV wall segments were not properly included even in the full-volume acquisition mode. In other patients (53 cases), the image quality was not good enough to ensure proper speckle tracking due to stitching artifacts or low spatial resolution, in which case the automatic tracing was not reliable. Patients for whom accurate strain values could not be obtained without manual correction were excluded from the analysis.

Of the 545 patients, 55 patients (10.1%) experienced the composite outcome of all-cause death or re-hospitalization due to acute decompensation of heart failure. There were 41 all-cause deaths (7.5%) and 14 rehospitalizations related to ADHF (2.6%). Compared with patients who did not experience these events, those who experienced these events show a significant difference in baseline characteristics (**Table 1**). Patients with the composite

Table 1. Baseline characteristics of the study population

Characteristics	Whole population (n = 545)	Event (+) (n = 55)	Event (−) (n = 490)	p-value
Clinical background				
Male sex	462 (84.8%)	43 (78.2%)	419 (85.5%)	0.151
Age	58.9 ± 12.7	71.2 ± 11.7	57.5 ± 12.0	< 0.001
SBP (mmHg)	135.4 ± 26.5	131.2 ± 26.2	135.9 ± 26.5	0.212
DBP (mmHg)	80.2 ± 18.9	75.2 ± 18.2	80.8 ± 18.9	0.037
BMI (kg/m²)	24.6 ± 3.0	23.1 ± 3.0	24.7 ± 2.9	< 0.001
Hypertension	249 (45.7%)	28 (50.9%)	221 (45.1%)	0.412
DM	120 (22.0%)	16 (29.1%)	104 (21.2%)	0.182
Dyslipidemia or statin user	173 (31.7%)	24 (43.6%)	149 (30.4%)	0.046
History of CVA	20 (3.7%)	6 (10.9%)	14 (2.9%)	0.010
History of MI	25 (4.6%)	2 (3.6%)	23 (4.7%)	0.722
Familial history of CAD	89 (16.3%)	6 (10.9%)	83 (16.9%)	0.251
Current smoker	231 (42.4%)	24 (43.6%)	207 (42.2%)	0.843
QRS duration > 120 ms	44 (8.1%)	10 (18.2%)	34 (6.9%)	0.008
Laboratory findings				
Hemoglobin (g/dL)	14.7 ± 1.7	13.6 ± 2.2	14.8 ± 1.6	< 0.001
Creatinine (mg/dL)	0.95 ± 0.40	0.35 ± 0.05	0.41 ± 0.02	0.157
Total cholesterol (mg/dL)	198.9 ± 49.4	178.3 ± 44.4	201.2 ± 49.4	< 0.001
Triglyceride (mg/dL)	183.6 ± 161.1	115.6 ± 69.0	191.2 ± 166.6	< 0.001
HDL cholesterol (mg/dL)	43.9 ± 10.7	43.2 ± 12.7	44.0 ± 10.5	0.580
LDL cholesterol (mg/dL)	119.9 ± 40.0	103.4 ± 41.0	121.8 ± 39.5	0.001
hs-CRP (mg/L)	0.81 ± 2.20	2.13 ± 4.60	0.66 ± 1.69	0.023
NT-proBNP (pg/mL)	613.9 ± 2,139.2	1,961.9 ± 5,120.4	487.0 ± 1,553.3	< 0.001
Peak CK-MB (ng/mL)	232.1 ± 201.6	300.2 ± 254.7	224.5 ± 193.5	0.037
Peak troponin I (ng/mL)	115.1 ± 110.4	181.5 ± 152.3	107.8 ± 102.3	0.001
Procedural and angiographic characteristics				
Mode of treatment				0.730
Primary PCI	505 (92.7%)	51 (92.7%)	454 (92.7%)	
Pharmacoinvasive therapy (thrombolysis followed by PCI)	24 (4.4%)	2 (3.6%)	22 (4.5%)	
Thrombolysis only	2 (0.4%)	0 (0%)	2 (0.4%)	
Emergent CABG	3 (0.6%)	0 (0%)	3 (0.6%)	
Urgent CABG after the PCI	1 (0.2%)	0 (0%)	1 (0.2%)	
Medical treatment only (e.g., STEMI due to severe vasospasm)	10 (1.8%)	2 (3.6%)	8 (1.6%)	

SBP: systolic blood pressure, DBP: diastolic blood pressure, BMI: body mass index, DM: diabetes mellitus, CVA: cerebrovascular accident, MI: myocardial infarction, CAD: coronary artery disease, ms: milliseconds, HDL: high-density lipoprotein, LDL: low-density lipoprotein, hs-CRP: high-sensitivity C-reactive protein, NT-proBNP: N-terminal pro b-type natriuretic peptide, CK-MB: creatine kinase-myocardial band, PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft, STEMI: ST-segment elevation myocardial infarction.

Table 2. Echocardiographic parameters of study population

Parameters	Whole population (n = 545)	Event (+) (n = 55)	Event (−) (n = 490)	p-value
Baseline 2D echocardiography				
LVEDD (mm)	48.1 ± 5.2	49.2 ± 6.1	48.0 ± 5.0	0.100
LVESD (mm)	33.1 ± 5.5	35.2 ± 7.2	32.9 ± 5.3	0.023
ISd (mm)	10.9 ± 1.9	11.0 ± 1.8	11.0 ± 1.9	0.879
PWd (mm)	10.1 ± 1.5	10.2 ± 1.6	10.1 ± 1.5	0.467
EDV (mL)	86.6 ± 22.8	94.1 ± 34.0	85.7 ± 21.1	0.079
ESV (mL)	42.2 ± 16.7	52.7 ± 27.6	41.0 ± 14.6	0.003
EF (%)	52.2 ± 8.8	46.0 ± 10.0	52.9 ± 8.3	< 0.001
LA dimension (M-mode, end-systolic, mm)	36.7 ± 4.6	38.1 ± 6.0	36.5 ± 4.4	0.070
LAVI (end-systolic, mL/m²)	33.0 ± 9.6	40.1 ± 11.4	32.2 ± 9.1	< 0.001
LVMI (g/m²)	103.7 ± 23.7	115.6 ± 28.2	102.3 ± 22.8	0.001
E/e'	11.6 ± 4.3	16.0 ± 6.4	11.1 ± 3.7	< 0.001
Estimated RVSP (mmHg)	27.5 ± 8.5	32.6 ± 14.2	26.8 ± 7.1	0.008
WMSI	1.56 ± 0.35	1.80 ± 0.35	1.54 ± 0.33	< 0.001
3D echocardiography				
Heart rate (/min)	69.5 ± 12.9	75.1 ± 16.1	68.9 ± 12.3	0.007
Frame rate (/min)	37.8 ± 8.9	35.2 ± 8.1	38.1 ± 9.0	0.026
EDV (mL)	93.8 ± 23.4	97.6 ± 33.3	93.3 ± 22.0	0.359
ESV (mL)	45.5 ± 16.8	54.9 ± 31.1	44.5 ± 14.1	0.018
EF (%)	53.4 ± 21.8	49.3 ± 10.3	53.8 ± 22.7	0.142
LVMI (g/m²)	73.3 ± 10.1	79.2 ± 13.3	72.7 ± 9.4	0.001
Strain analysis				
2D GLS (peak systolic strain, %)	−13.40 ± 3.99	−10.91 ± 3.98	−13.71 ± 3.89	< 0.001
3D GLS	−9.60 ± 3.18	−8.01 ± 2.92	−9.77 ± 3.17	< 0.001
3D GCS	−11.55 ± 5.16	−9.76 ± 4.30	−11.75 ± 5.21	0.007
3D GRS	24.79 ± 9.14	20.84 ± 9.49	25.24 ± 9.01	0.001
3D GAS	−17.69 ± 5.6	−14.96 ± 5.93	−18.00 ± 5.48	< 0.001

LVEDD: left ventricular end-diastolic dimension, LVESD: left ventricular end-systolic dimension, ISd: interventricular septal thickness at end-diastole, PWd: posterior wall thickness at end-diastole, EDV: end-diastolic volume, ESV: end-systolic volume, EF: ejection fraction, LA: left atrium, LAVI: left atrium volume index, LVMI: left ventricular mass index, E/A ratio: ratio between peak early filling (E-wave) and late diastolic (A-wave) velocities, DT: deceleration time of early filling velocity, RVSP: right ventricular systolic pressure, RWMA: regional wall motion abnormality, WMSI: wall motion score index, 3D: three-dimensional, GLS: global longitudinal strain, GCS: global circumferential strain, GRS: global radial strain, GAS: global area strain.

outcomes were older, more likely to have lower BMI, higher prevalence of dyslipidemia or history of cerebrovascular accident. The prevalence of prolonged QRS duration was also higher in clinical event group. Serum hemoglobin, total serum cholesterol, triglyceride and low-density lipoprotein (LDL) cholesterol were lower in the event group, while hs-CRP, NT-proBNP, peak CK-MB, and peak troponin I were elevated in the event group. (all, p < 0.05)

There were also differences between these two groups in terms of echocardiographic parameters (**Table 2**). Systolic and diastolic dysfunction, along with left atrial enlargement and LV hypertrophy, was more prominent in patients who experienced events than in those who did not experience events. The infarct extent assessed by wall motion score index was also wider in patients with events, which agreed with the higher mean peak value of troponin I in these patients. (all, p < 0.05)

The systolic peak value of 2D GLS was understandably lower in patients with events. Similarly, the 3D strain parameters such as GAS, GCS and GLS were also lower in patients with events. On the other hand, in the case of 3D GRS, which is an index reflecting the degree of systolic thickening of the LV wall, the value was small in patients who experienced events (**Table 2**).

### Diagnostic performance of the 3D echocardiographic parameters
Figure 1 compares the overall diagnostic power of the 3D strain. The highest value of area under the curve among 3D global strain parameters was 3D GLS, although the difference
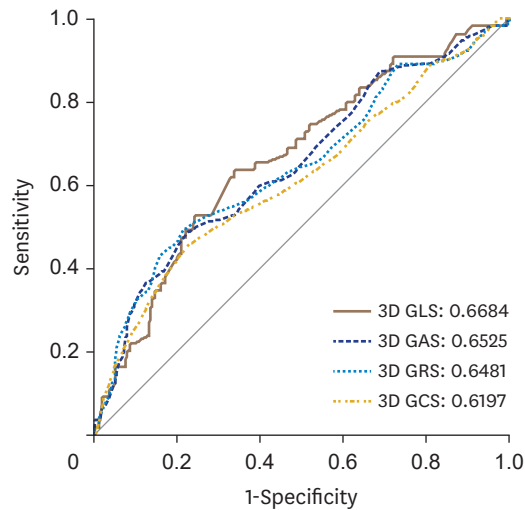
Figure 1. Diagnostic performances of the various 3D global strain values during follow-up period.
3D: three-dimensional, GAS: global area strain.

between these parameters were not statistically significant (**Figure 1**). When compared with LV EF and 2D GLS, 3D GLS showed similar predictive performance (**Figure 2**).

The best cut-off values which maximize the sensitivity and specificity of each parameters were obtained. The best cut-off values for 2D and 3D LV EF were 47% and 41%, with the HR of 3.04 and 6.04 and the C-index of 0.838 and 0.892, respectively. Best cut-off values for 2D GLS and 3D GLS were both 9. The HR of 2D GLS and 3D GLS were 5.49 and 1.97, with the C-index of 0.848 and 0.819, respectively. Best cut-off values for 2D left ventricle mass index (LVMI) and 3D LVMI were 96 and 91. The HR of 2D LVMI and 3D LVMI were 0.47 and 0.39, with the C-index of 0.824 and 0.829, respectively (**Table 3**). There were significant differences between the groups divided by each echocardiographic parameter, regardless of the parameters (**Figure 3**).
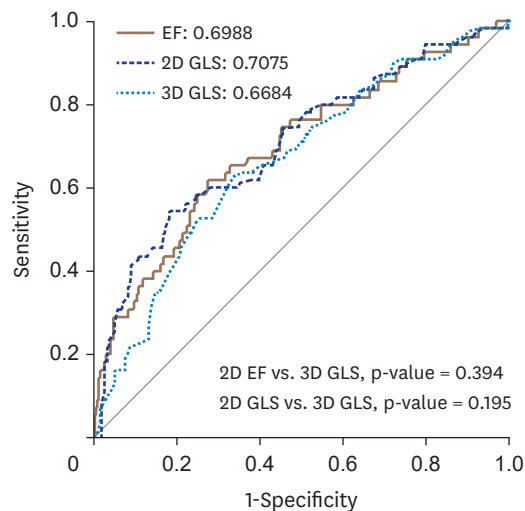
Figure 2. The AUC curve: comparison of EF, 2D GLS, and 3D GLS.
AUC: area under the curve, EF: ejection fraction, 2D: two-dimensional, GLS: global longitudinal strain, 3D: three-dimensional.

Table 3. Best cut-off values for EF, 2D GLS, and 3D GLS derived from Cox proportional hazard model

Variables	Cut-off value	Adjusted HR	95% CI for HR	C-index	95% CI for C-index
2D EF	47	3.76	2.04–6.90	0.848	0.797–0.899
3D EF	45	2.85	1.54–5.31	0.834	0.796–0.892
2D GLS	9	5.5	3.01–10.04	0.852	0.802–0.902
3D GLS	9	2.21	1.18–4.14	0.826	0.773–0.879
2D LVMI	96	0.47	0.24–0.93	0.824	0.768–0.881
3D LVMI	86	0.385	0.20–0.75	0.829	0.773–0.882

Baseline Cox proportional hazards models are constructed using various clinical indicators and the overall predictive power of the models are expressed using Harrell's C index.
EF: ejection fraction, 2D: two-dimensional, GLS: global longitudinal strain, 3D: three-dimensional, HR: hazard ratio, CI: confidence interval; LVMI: left ventricle mass index.
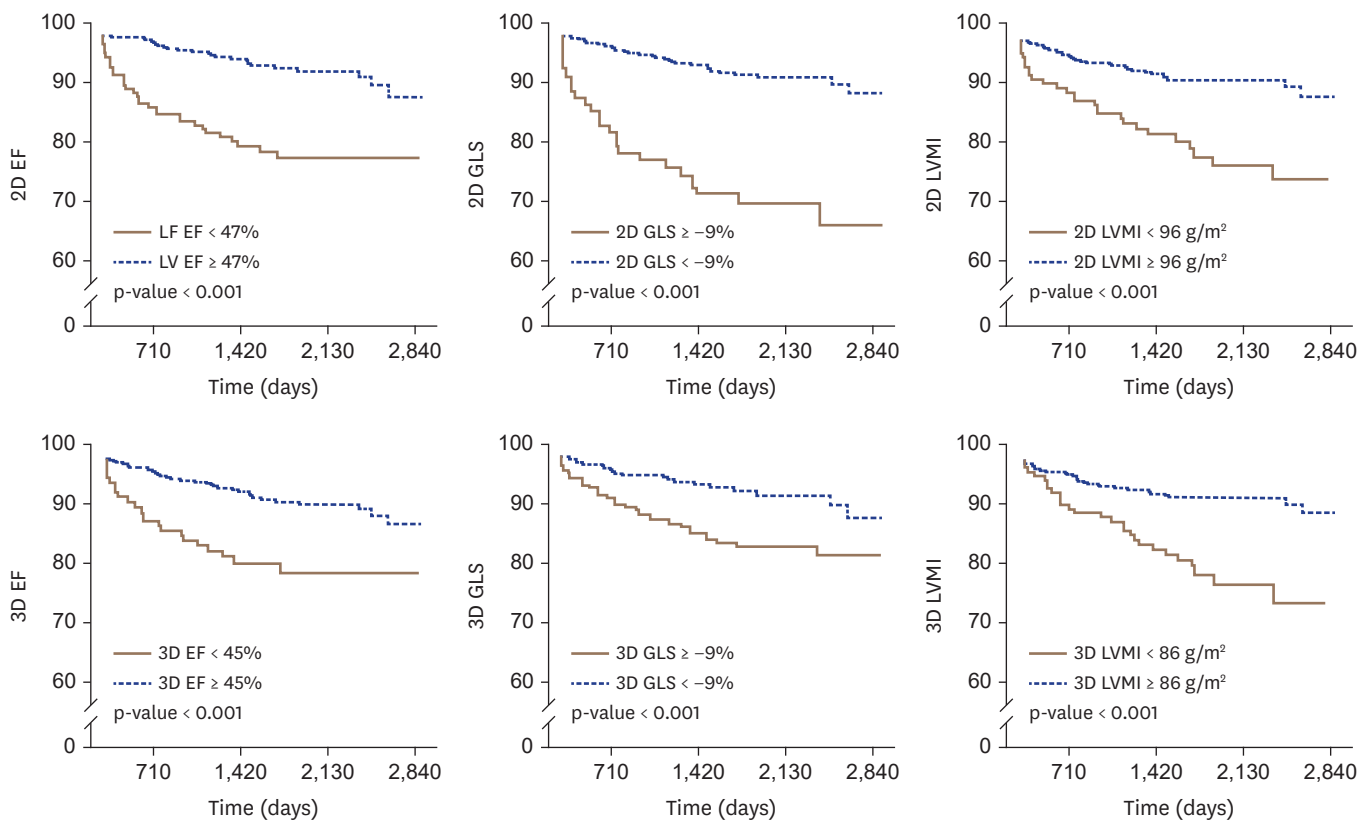
Figure 3. Kaplan-Meier analysis of composite outcome according to each echocardiographic parameters; 2D EF, 2D GLS, 2D LVMI, 3D EF, 3D GLS, 3D LVMI.
2D: two-dimensional, EF: ejection fraction, GLS: global longitudinal strain, LVMI: left ventricle mass index, 3D: three-dimensional.

Kaplan-Meier analysis demonstrated the significant differences of the occurrence of composite outcomes according to each parameter (**Figure 3**).

The maximum likelihood ratio test for various prognostic models

The maximum likelihood ratio test was performed to evaluate the additional prognostic value of strain indices over conventional prognostic model including baseline clinical parameters and LV EF. When LV EF, 2D GLS or 3D GLS was added to basic model consisting of clinical and laboratory parameters, the diagnostic performances of models were significantly improved. (all, p-value < 0.05) However, when comparator model was set to include not only baseline characteristics but LV EF, 2D GLS only demonstrated a significant improvement of predicting model (**Table 4**).

Table 4. The maximum LR of various predicting models

Follow-up duration	Baseline model vs. baseline model + LV EF		Baseline model vs. baseline model + 2D GLS		Baseline model vs. baseline model + 3D GLS		Baseline model + LV EF vs. baseline model + LV EF + 2D GLS		Baseline model + LV EF vs. baseline model + LV EF + 3D GLS	
	LR	p-value	LR	p-value	LR	p-value	LR	p-value	LR	p-value
1 year	32.7	< 0.001	23.2	< 0.001	5.0	0.02	6.2	0.01	0.25	0.61
2 years	19.9	< 0.001	27.4	< 0.001	4.8	0.03	11.7	< 0.001	0.86	0.35
4 years	18.7	< 0.001	27.0	< 0.001	6.5	0.01	12.3	< 0.001	1.76	0.18
End of follow-up	15.1	< 0.001	29.1	< 0.001	5.6	0.02	15.9	< 0.001	1.49	0.22

LR: likelihood ratio, LV: left ventricle; EF: ejection fraction, 2D: two-dimensional, GLS: global longitudinal strain, 3D: three-dimensional.

DISCUSSION

Over the past several years, efforts have been made to demonstrate the clinical usefulness of 3D strain indices. However, in contrast to the 2D strain, the clinical usefulness of which has been verified based on extensive clinical experience,[5] more research is still needed to determine the role of the 3D strain in patients with cardiovascular diseases. Only a very small number of previous studies have suggested the 3D strain can be used as a useful index for assessing the prognosis of patients with ischemic heart disease.[16)17] In this context, this study presented data that could evaluate the clinical implications of the 3D global strain, especially in STEMI patients.

Since it is not always possible to obtain high-quality volumetric data that are optimal for image analysis in all patients, the feasibility of the application of 3D global strain in daily practice remains questionable.[11)18] Previous studies reported that reliable 3D strain analysis was only available in 60%–80% of patients.[19)20] However, 3D strain analysis was available in most cases in this study. In our study, proper 3D strain analysis could not be performed in only 13.8% of all patients, due to issues such as poor acoustic window, large LV size, and inadequately low image resolution.

Also, 3D echocardiographic parameters demonstrated good correlation with 2D echocardiographic parameters. The correlation was constantly fair among the various parameters, including volumetric values such as LV EDV, LV ESV, LVMI and functional parameters like LV EF and GLS, irrespective of adverse outcome. This observation is concordant with previous studies that also reported close correlations between 2D and 3D global longitudinal strain.[12)19]

3D strain values which represent myocardial shortening were significantly higher, while 3D GRS which reflects thickening of LV wall was significantly lower in patients with adverse outcomes. This finding is uniformly observed among various duration of follow-up, although the relative risks were slightly diminished as follow-up duration was elongated. Among 3D strain values, 3D GLS had the highest diagnostic performance of the adverse outcomes. Other 3D strain values such as 3D GCS or 3D GRS demonstrated slightly inferior diagnostic performances throughout the follow-up periods. This may be partly due to the fact that the reproducibility of these parameters is not as good as that of 3D GLS or 3D GAS. The intraobserver and interobserver variability of GRS was poorer than that of GLS or GCS in 3D strain analysis.[21)22] In several other studies that reported the prognostic value of 3D strain parameters, 3D GAS or 3D GLS were predicted the adverse outcome or LV remodeling.[16)17]

It is also noteworthy that 3D strain values did not predict the occurrence of adverse outcomes better than 2D strains in STEMI patients, different from our expectation. In this study, we

constructed models that predicted the patients' prognosis by adding LV EF, 2D GLS, or 3D GLS to various other clinical parameters. Furthermore, we investigated whether 3D strain analysis could improve the overall predictive power of statistical models. Three-dimensional strain values demonstrated significant differences in univariate analyses and multivariate analysis consisting of clinical parameters, along with LV EF or 2D GLS. And 3D GLS significantly improved predictive power of model when it was added to a baseline model with clinical parameters. However, in a model with clinical parameters and LV EF, adding 3D GLS to the model did not significantly improved the predictive power of the model, unlike 2D GLS that had additional prognostic importance even with the LV EF.

Several explanations are possible. First, spatial and temporal resolution or the image acquisition rate of 3D strain imaging is still lower than those of 2D strain.[12] And 3D strain values in healthy subjects were influenced not only by image quality and temporal resolution but also LV volumes.[23] Although the volume rate of strain in our study was 37.8 ± 8.9 per second which is considered to be fair in evaluation of 3D strain,[12] there still remains the possibility of suboptimal evaluation of 3D strains due to relatively low volume rate when it is compared with 2D strain.

Inter-vendor variability and low levels of validation are also important issues to be addressed. Since post-processing steps can vary among vendors, the reference values are not unified, and each vendor has its own reference values.[11)24)] This confusing state make the evaluation and validation process of 3D strain difficult. If the 3D strain values could be widely used in clinical environment, researches should be focus on common reliable methods to measure 3D strain values regardless of the commercial vendor system.

Some limitations are worth mentioning. First, patients with STEMI who did not stay in sinus rhythm were excluded from this study. The 3D strain has an inherent limitation that it cannot be performed in patients with significant heart rate variability due to problems such as atrial fibrillation or frequent ectopic beats.[25] Moreover, 3D image quality was poor in some patients, and 3D strain analysis could not be performed accurately even if the number was not large. Three-dimensional analysis has the advantage of being able to simultaneously analyze LV volume, LV EF, and LV mass as well as most LV strain components,[10)25)26)] however, these weak points cause the 3D strain to have lower feasibility than the 2D GLS. Second, this study excluded patients who died during hospitalization or had severe cardiogenic shock. Thus, the incidence of adverse events was slightly low compared to other STEMI studies. Third, the question of when to perform an echocardiographic examination in the hospital course of patients with STEMI remains to be determined. The general recommendation merely states that a comprehensive evaluation should be carried out within two weeks.[26] To date, no study has yet mentioned the optimal time frame for 2D and 3D imaging. Even in the context of successful revascularization, 3D strain analysis may be affected in some patients by problems such as myocardial stunning or microvascular obstruction.[27] Previous strain studies have used different time frames for image acquisition, but most of them underwent echocardiography within two days.[2)5)28)]

Theoretically, although 3D strain can overcome the limitations of 2D strain and has lots of advantages, but considering technical problems such as lower feasibility with worse reproducibility, more time consuming, and difficulty in arrhythmia, there will still need to be more technical improvements to be used in clinical practice.

In conclusion, 3D global strain values could be reliably measured in the majority of the patients and had a significant prognostic value. However, the predictive power of the 3D strain values was lower than that of the 2D strain. The clinical implications of 3D strain indices should be investigated further.

REFERENCES

1. Gorcsan J 3rd, Tanaka H. Echocardiographic assessment of myocardial strain. *J Am Coll Cardiol* 2011;58:1401-13.
   PUBMED | **CROSSREF**

2. Mollema SA, Delgado V, Bertini M, et al. Viability assessment with global left ventricular longitudinal strain predicts recovery of left ventricular function after acute myocardial infarction. *Circ Cardiovasc Imaging* 2010;3:15-23.
   PUBMED | **CROSSREF**

3. Antoni ML, Mollema SA, Atary JZ, et al. Time course of global left ventricular strain after acute myocardial infarction. *Eur Heart J* 2010;31:2006-13.
   PUBMED | **CROSSREF**

4. Hung CL, Verma A, Uno H, et al. Longitudinal and circumferential strain rate, left ventricular remodeling, and prognosis after myocardial infarction. *J Am Coll Cardiol* 2010;56:1812-22.
   PUBMED | **CROSSREF**

5. Ersbøll M, Valeur N, Mogensen UM, et al. Prediction of all-cause mortality and heart failure admissions from global left ventricular longitudinal strain in patients with acute myocardial infarction and preserved left ventricular ejection fraction. *J Am Coll Cardiol* 2013;61:2365-73.
   PUBMED | **CROSSREF**

6. Cha MJ, Kim HS, Kim SH, Park JH, Cho GY. Prognostic power of global 2D strain according to left ventricular ejection fraction in patients with ST elevation myocardial infarction. *PLoS One* 2017;12:e0174160.
   PUBMED | **CROSSREF**

7. Antoni ML, Mollema SA, Delgado V, et al. Prognostic importance of strain and strain rate after acute myocardial infarction. *Eur Heart J* 2010;31:1640-7.
   PUBMED | **CROSSREF**

8. Wang N, Hung CL, Shin SH, et al. Regional cardiac dysfunction and outcome in patients with left ventricular dysfunction, heart failure, or both after myocardial infarction. *Eur Heart J* 2016;37:466-72.
   PUBMED | **CROSSREF**

9. Kalam K, Otahal P, Marwick TH. Prognostic implications of global LV dysfunction: a systematic review and meta-analysis of global longitudinal strain and ejection fraction. *Heart* 2014;100:1673-80.
   PUBMED | **CROSSREF**

10. Seo Y, Ishizu T, Aonuma K. Current status of 3-dimensional speckle tracking echocardiography: a review from our experiences. *J Cardiovasc Ultrasound* 2014;22:49-57.
    PUBMED | **CROSSREF**

11. Badano LP, Cucchini U, Muraru D, Al Nono O, Sarais C, Iliceto S. Use of three-dimensional speckle tracking to assess left ventricular myocardial mechanics: inter-vendor consistency and reproducibility of strain measurements. *Eur Heart J Cardiovasc Imaging* 2013;14:285-93.
    PUBMED | **CROSSREF**

12. Negishi K, Negishi T, Agler DA, Plana JC, Marwick TH. Role of temporal resolution in selection of the appropriate strain technique for evaluation of subclinical myocardial dysfunction. *Echocardiography* 2012;29:334-9.
    PUBMED | **CROSSREF**

13. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013;61:e78-140.
    PUBMED | **CROSSREF**

14. Lang RM, Badano LP, Tsang W, et al. EAE/ASE recommendations for image acquisition and display using three-dimensional echocardiography. *Eur Heart J Cardiovasc Imaging* 2012;13:1-46.
    PUBMED | **CROSSREF**

15. Hicks KA, Tcheng JE, Bozkurt B, et al. 2014 ACC/AHA key data elements and definitions for cardiovascular endpoint events in clinical trials: a report of the American College of Cardiology/American

Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Cardiovascular Endpoints Data Standards). *Circulation* 2015;132:302-61.
PUBMED | **CROSSREF**

16. Abate E, Hoogslag GE, Antoni ML, et al. Value of three-dimensional speckle-tracking longitudinal strain for predicting improvement of left ventricular function after acute myocardial infarction. *Am J Cardiol* 2012;110:961-7.
PUBMED | **CROSSREF**

17. Shin SH, Suh YJ, Baek YS, et al. Impact of area strain by 3D speckle tracking on clinical outcome in patients after acute myocardial infarction. *Echocardiography* 2016;33:1854-9.
PUBMED | **CROSSREF**

18. Jasaityte R, Heyde B, Ferferieva V, et al. Comparison of a new methodology for the assessment of 3D myocardial strain from volumetric ultrasound with 2D speckle tracking. *Int J Cardiovasc Imaging* 2012;28:1049-60.
PUBMED | **CROSSREF**

19. Reant P, Barbot L, Touche C, et al. Evaluation of global left ventricular systolic function using three-dimensional echocardiography speckle-tracking strain parameters. *J Am Soc Echocardiogr* 2012;25:68-79.
PUBMED | **CROSSREF**

20. Hayat D, Kloeckner M, Nahum J, et al. Comparison of real-time three-dimensional speckle tracking to magnetic resonance imaging in patients with coronary heart disease. *Am J Cardiol* 2012;109:180-6.
PUBMED | **CROSSREF**

21. Saito K, Okura H, Watanabe N, et al. Comprehensive evaluation of left ventricular strain using speckle tracking echocardiography in normal adults: comparison of three-dimensional and two-dimensional approaches. *J Am Soc Echocardiogr* 2009;22:1025-30.
PUBMED | **CROSSREF**

22. Luis SA, Yamada A, Khandheria BK, et al. Use of three-dimensional speckle-tracking echocardiography for quantitative assessment of global left ventricular function: a comparative study to three-dimensional echocardiography. *J Am Soc Echocardiogr* 2014;27:285-91.
PUBMED | **CROSSREF**

23. Muraru D, Cucchini U, Mihăilă S, et al. Left ventricular myocardial strain by three-dimensional speckle-tracking echocardiography in healthy subjects: reference values and analysis of their physiologic and technical determinants. *J Am Soc Echocardiogr* 2014;27:858-871.e1.
PUBMED | **CROSSREF**

24. Gayat E, Ahmad H, Weinert L, Lang RM, Mor-Avi V. Reproducibility and inter-vendor variability of left ventricular deformation measurements by three-dimensional speckle-tracking echocardiography. *J Am Soc Echocardiogr* 2011;24:878-85.
PUBMED | **CROSSREF**

25. Jasaityte R, Heyde B, D'hooge J. Current state of three-dimensional myocardial strain estimation using echocardiography. *J Am Soc Echocardiogr* 2013;26:15-28.
PUBMED | **CROSSREF**

26. Prastaro M, Pirozzi E, Gaibazzi N, et al. Expert review on the prognostic role of echocardiography after acute myocardial infarction. *J Am Soc Echocardiogr* 2017;30:431-443.e2.
PUBMED | **CROSSREF**

27. Huttin O, Zhang L, Lemarié J, et al. Global and regional myocardial deformation mechanics of microvascular obstruction in acute myocardial infarction: a three dimensional speckle-tracking imaging study. *Int J Cardiovasc Imaging* 2015;31:1337-46.
PUBMED | **CROSSREF**

28. Munk K, Andersen NH, Terkelsen CJ, et al. Global left ventricular longitudinal systolic strain for early risk assessment in patients with acute myocardial infarction treated with primary percutaneous intervention. *J Am Soc Echocardiogr* 2012;25:644-51.
PUBMED | **CROSSREF**