Research Square

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Evaluation of Extracellular Volume by Computed Tomography is Useful for Prediction of Prognosis in Dilated Cardiomyopathy

Satomi Yashima
Chiba University Graduate School of Medicine School of Medicine: Chiba Daigaku Daigakuin Igaku Kenkyuin Igakubu

Hiroyuki Takaoka (tapy21century@yahoo.co.jp)
Chiba University Graduate School of Medicine School of Medicine: Chiba Daigaku Daigakuin Igaku Kenkyuin Igakubu https://orcid.org/0000-0001-9938-2405

Manami Takahashi
Chiba University Graduate School of Medicine School of Medicine: Chiba Daigaku Daigakuin Igaku Kenkyuin Igakubu

Makiko Kinoshita
Chiba University Graduate School of Medicine School of Medicine: Chiba Daigaku Daigakuin Igaku Kenkyuin Igakubu

Haruka Sasaki
Chiba University Graduate School of Medicine School of Medicine: Chiba Daigaku Daigakuin Igaku Kenkyuin Igakubu

Noriko Suzuki-Eguchi
Chiba University Graduate School of Medicine School of Medicine: Chiba Daigaku Daigakuin Igaku Kenkyuin Igakubu

Joji Ota
Chiba University Hospital: Chiba Daigaku Igakubu Fuzoku Byoin

Yusei Nishikawa
Chiba University: Chiba Daigaku

Hiroki Goto
Chiba University Graduate School of Medicine School of Medicine: Chiba Daigaku Daigakuin Igaku Kenkyuin Igakubu

Yoshio Kobayashi
Chiba University Graduate School of Medicine School of Medicine: Chiba Daigaku Daigakuin Igaku Kenkyuin Igakubu

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Abstract

Purpose:

Dilated cardiomyopathy (DCM) is commonly encountered in daily clinical practice, and screening for coronary artery disease and other cardiomyopathies is necessary for its diagnosis. Cardiac CT is useful for the screening of coronary artery stenosis, and extracellular volume fraction (ECV) analysis by CT has become available using new specific software. Here, we evaluated the utility of ECV analysis using cardiac CT to predict patient prognosis in cases with DCM.

Methods:

We analyzed 70 cases with DCM and coronary computed tomography (CT) with available late-phase images. We evaluated the ECV of the left ventricular myocardium (LVM) using commercially available software (Ziostation 2, Ziosoft Inc, Japan).

Results:

ECV on LVM was 34.5±4.9%. Major adverse cardiac events (MACE) occurred in 20 cases (29%). ECV of the LVM on CT and the presence of significant valvular disease were significantly higher in cases with MACE than in those without (37.6±5.9 vs 33.2±3.9% and 55% vs 24%, P=0.0057 and P=0.013). LVEF was significantly lower in cases with MACE than in those without (22.3±7.6 vs 30.8±11.8%, P=0.0008). The best cut-off value of ECV on LVM for prediction of MACE was 32.7% based on receiver operating characteristics analysis. Cases with ECV ≥32.7% had significantly higher MACE based on Kaplan-Meier analysis (P=0.012). Only ECV on LVM was an independent predictor of MACE based on a Cox proportional hazards model (P=0.028).

Conclusion:

Evaluation of ECV on LVM by CT is useful for predicting MACE in patients with DCM.

Background

Dilated cardiomyopathy (DCM) is commonly encountered in daily clinical practice. It is the third-most common reason for heart failure and has an estimated prevalence of one in 2500 in the average population (1). Diagnosis is dependent on screening for coronary artery disease, other cardiomyopathies and other conditions causing abnormal loading, including valvular heart disease and hypertension (1) (2) (3).

The gold standard for evaluation of myocardial damage is late enhancement analysis using cardiac magnetic resonance imaging (MRI). The pattern of late gadolinium enhancement (LGE) is useful in the differential diagnosis of several types of cardiomyopathies 4). Linear mid-layer LGE is the typical pattern in patients with DCM and the presence of the LGE has been regarded as a sign of worse prognosis in these patients (5) (6).

Of interest, extracellular volume fraction (ECV) analysis using T1 mapping images on MRI is also useful for quantitative analysis of myocardial damage. This analysis requires gadolinium contrast (7). ECV provides significant prognostic information in DCM, and patients with adverse events have significantly higher ECV than those without 8).

Cardiac MRI is sometimes contraindicated in patients with cardiovascular disease, because of the presence of cardiac mechanical devices, claustrophobia or severe renal dysfunction, and obtaining clear LGE images in cases with arrhythmia is often difficult (9). Cardiac computed tomography (CT) is useful for screening coronary artery stenosis in patients suspected of having myocardial disease (10), and obtaining clear cardiac images is easy even in cases with arrhythmia (11). Additional late phase scan is also helpful for detecting myocardial damage as late enhancement (12). New software has also now made ECV analysis on CT available, and ECV values on CT are similar to those on MRI (13).

The purpose of this study was to evaluate the utility of ECV analysis on CT in predicting major adverse cardiac events (MACE) in patients with DCM.

Methods

Ninety-three patients diagnosed with DCM underwent coronary computed tomography (CT), including late-phase acquisition in our institution from Dec 2008 to Feb 2021. However, ECV analysis was impossible because of the significant metallic artifacts of pacemaker leads in 4 patients, significant gaps of the cardiac phases between the non-contrast and late phase cardiac images in 2 patients, and the different tube voltages between the non-contrast and late phase cardiac images in 17 patients. The study was conducted under a retrospective design in the remaining 70 consecutive patients with DCM. Written informed consents were obtained from all patients. All patients had a lower left ventricular (LV) ejection fraction (LVEF) less than 45%, and they were finally diagnosed with DCM based on the screening for coronary artery disease, other cardiomyopathies, and other conditions causing abnormal loading, including primary valvular heart disease and hypertension (2). Major adverse cardiac events (MACE) were defined as a composite of cardiovascular death; fatal arrhythmic events, including ventricular tachycardia or fibrillation; stroke; and hospitalization due to heart failure. Patient background, including risk factors for coronary artery disease and medical treatment, were obtained from medical records (Table 1).

Table 1
Details of patient background

	N=70
Age, years	58 ± 14
Male, n (%)	52 (74)
Hypertension, n (%)	30 (43)
Dyslipidemia, n (%)	22 (31)
Diabetes Mellitus, n (%)	15 (22)
Atrial fibrillation, n (%)	14 (20)
Administration of β-blocker, n (%)	44 (63)
Administration of ARB, n (%)	24 (34)
Administration of ACE-I, n (%)	23 (33)
Administration of MRB (%)	27 (39)
Administration of statin, n (%)	20 (29)
Administration of SGLT-2, n (%)	0 (0)
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor II blocker; SGLT-2, sodium-dependent glucose cotransporter 1; MRB, mineralocorticoid receptor antagonists	

Protocol for computed tomography

CT was performed using a 320-slice CT (Aquilion One or Aquilion One/ViSion Edition, Canon Medical Systems, Otawara, Japan) or 256-slice CT (Revolution CT, GE Healthcare, GE Healthcare, Milwaukee, Wis), with patients lying supine on the scanner table. A scout scan and a non-contrast ECG-gated cardiac scan were performed using a prospective ECG-gated technique before contrast scan. Slice thickness and tube voltage was 0.5 mm and 80-120 kV for 320-slice CT, and 0.625 mm and 70 kV for 256-slice CT, respectively (Table 1)

For retrospective ECG gating, performed using the dose modulation technique to decrease radiation dose during the systolic phases where possible, conventional enhanced CT was performed with a slice thickness and tube voltage of 0.5 mm and 80-120 kV for 320-slice CT and 0.625 mm and 120 kV for 256-slice CT, respectively (Table 1) (14). Tube current at scanning was determined based on the auto exposure control system with slight manual modification. All patients with a heart rate ≥65 beats per minute received 10 mg of propranolol or 12.5 mg landiolol prior to scanning, except for those in whom β-blockers were contraindicated. Just prior to the scanning procedure, subjects were administered two doses of isosorbide dinitrate sublingually.

For contrast material injection, we employed a routine triphasic protocol. Right or left antecubital intravenous access using a 20- or 22-gauge needle was attained, and the system was connected to a dual-syringe injector with a dual-flow option (Dual Shot, Nemoto, Tokyo, Japan). During the first phase, we injected 50–70 ml of undiluted iodinate contrast agent (350-370mg/mL) at 3-4 ml/s, followed by 40-50 ml of a 50%/50% saline-to-contrast material mixture at 3-4 ml/s and 20 ml of pure saline at 4 ml/s.

A late phase scan was added 6 minutes after the injection of iodine contrast media using the prospective ECG-gating technique, slightly modified from similar previous research (15) (Figure 1). CT was performed with a slice thickness and tube voltage of 0.5 mm and 80-120 kV for 320-slice CT and 0.625 mm and 70 kV for 256-slice CT, respectively (Figure 1) (same tube voltage as for the non-contrast scan).

Analysis of ECV on CT

Myocardial ECV of the left ventricular myocardium (LVM) was measured using commercially available software (Ziostation 2, Ziosoft Inc, Japan) with the following equation: ECV= (ΔHUm/ΔHUb)/(1 − Hct), where ΔHUm is change in myocardial CT attenuation in Hounsfield units (HU), ΔHUb is change in CT attenuation of the blood, and Hct is hematocrit (15) (Figure 2). This software performs automatic three-dimensional non-rigid registration of the myocardium between non-contrast and late phase CT images to generate subtraction images (16). The change in CT attenuation (ΔHU) is then obtained on the subtraction image. The software produces a polar map showing both 16 American Heart Association myocardial segments with the mean ECV value for each segment and the mean ECV value of all LVM. ECV of LVM was measured by two cardiologists (SA and YN). The effective dose for scanning of coronary arteries was calculated from the dose-length product in a dose report (conversion factor 0.014) (17).

Statistical analysis

Continuous variables are expressed as the mean ± SD or as median (interquartile range) if not normally distributed. Categorical variables are reported as counts and percentages. All tests were 2-sided, and p values <0.05 were considered to indicate statistical significance. Analysis of variance or chi-square tests were used to compare baseline characteristics. Interobserver agreement over the presence of significant coronary artery stenosis was assessed using correlation coefficients and compared using chi-square tests. All statistical analyses were performed using the JMP software program, version 15.0.0 (SAS Institute Inc, Cary, NC, USA).

Results

Patients were followed for 53 ± 44 months after the performance of cardiac CT. Among the 20 patients (28.6%) who experienced MACE during the follow-up period, the number of patients taking mineralocorticoid receptor antagonists (MRB) was significantly higher than the number not taking these agents (60% vs 30%, P=0.020). (Table 2). ECV of the LVM on CT was significantly higher in cases with

MACE than in those without MACE (37.6±5.9 vs 33.2±3.9%, P=0.0057). The presence of significant valvular disease (≥moderate) was significantly higher in cases with MACE than in those without MACE (55% vs 24%, P=0.013). LVEF was significantly lower in cases with MACE than in those without MACE (22.3±7.6 vs 30.8±11.8%, P=0.0008).

Table 2
Comparison of patient background between patients with and without major adverse cardiac events

	MACE (+) (N=20)	MACE (-) (N=50)	P-value
Age, years	57 ± 12	58 ± 14	0.95
Male, n (%)	16 (80)	36 (72)	0.49
Hypertension, n (%)	6 (30)	24 (48)	0.17
Dyslipidemia, n (%)	5 (25)	17 (34)	0.46
Diabetes Mellitus, n (%)	2 (10)	13 (27)	0.13
Atrial fibrillation, n (%)	4 (20)	10 (20)	1.0
Administration of β-blocker, n (%)	13 (65)	31 (62)	0.81
Administration of statin, n (%)	6 (30)	14 (28)	0.87
Administration of ACE-i or ARB, n (%)	13 (65)	33 (66)	0.94
Administration of MRB, n (%)	12 (60)	15 (30)	0.020*
Follow-up period (months)	46 ± 34	55 ± 47	0.34

ACE, angiotensin converting enzyme; ARB, angiotensin receptor II blocker; MRB, mineralocorticoid receptor antagonists

Table 3
Comparison of parameters on TTE and CT between patients with and without major adverse cardiac events

	MACE (+) (N=20)	MACE (-) (N=50)	P-value
LVEF on TTE (%)	22 ± 8	31 ± 12	0.0008*
Significant valvular disease (≥moderate) on TTE, n (%)	11 (55%)	12 (24%)	0.013*
ECV of LVM on CT	38 ± 5.9	33 ± 3.9	0.0057*

LVEF, left ventricular ejection fraction; LVM, left ventricular myocardium; TTE, transthoracic echocardiography; ECV, extracellular volume fraction

The best cut-off value of ECV on LVM for prediction of MACE was 32.7% based on receiver operating characteristics (ROC) analysis. The area under the curve (AUC) of the ROC curve was 0.751 (P=0.0034)

(Figure 3A). Sensitivity and specificity for prediction of future MACE were 90% and 54%, respectively (Figure 3A). The best cut-off value for left ventricular ejection fraction for prediction of MACE was 24% based on ROC analysis. The area under the curve of the receiver operating characteristics curve was 0.718 (P=0.0026). Sensitivity and specificity for prediction of future MACE were 75% and 68%, respectively. (Figure 3B)

Cases with ECV ≥32.7% had significantly higher MACE than those with <32.7% during the follow-up period based on Kaplan-Meier analysis (Figure 4). The consistency of ECV of LVM on CT between the two observers was 0.85. A univariate Cox proportional hazards model showed that significant valvular disease (≥moderate) on TTE, LVEF on TTE ≤ 24%, administration of MRB and ECV of LVM on CT ≥ 32.7% were significant risk factors for MACE (P=0.025, 0.0089, 0.018 and 0.0044) (Table 4). A multivariate Cox proportional hazard model was also performed, and ECV of LVM on CT ≥ 32.7% was the only independent significant predictor of MACE during the follow-up period (P=0.78, 0.15, 0.49 and 0.028) (Table 5). The effective radiation dose for additional late phase scan was 3.7±0.4mSv (radiation dose for the first 8 cases was not recorded, and these were excluded from this analysis).

Table 4

	Hazard ratio	95% Confidence interval	P value
Significant valvular disease (≥moderate) on TTE, n (%)	2.76	1.13 – 6.73	0.025*
LVEF on TTE ≤ 24% (%)	3.88	1.41 – 10.7	0.0089*
Administration of MRB, n (%)	2.99	1.21 – 7.38	0.018*
ECV on LVM ≥ 32.7% (%)	8.42	1.94 – 36.5	0.0044*
TTE, transthoracic echocardiography; LVEF, left ventricular ejection fraction; MRB, mineralocorticoid receptor antagonists; ECV, extra-cellular volume fraction; LVM, left ventricular myocardium			

Table 5

	Hazard ratio	95% Confidence interval	P value
Significant valvular disease (≥moderate) on TTE, n (%)	1.15	0.43 – 3.1	0.78
LVEF on TTE ≤24% (%)	2.29	0.74 – 7.1	0.15
Administration of MRB, n (%)	1.41	0.53 – 3.8	0.49
ECV on LVM ≥32.7% (%)	5.62	1.20 – 26.3	0.028*
TTE, transthoracic echocardiography; LVEF, left ventricular ejection fraction; MRB, mineralocorticoid receptor antagonists; ECV, extra-cellular volume fraction; LVM, left ventricular myocardium			

Discussion

The results of this study suggest that ECV of LVM on CT might be a predictor of future MACE in patients with DCM. CT is useful for the detection of coronary artery stenosis, and ECV analysis is also feasible if an additional late phase scan is performed. From these findings, CT appears to be a useful modality for whole cardiac screening in patients with DCM. (6)

ECV analysis in cases on DCM

The presence of LGE is a marker of higher risk of future cardiac events in patients with DCM, because myocardial damage is a marker of low cardiac function and fatal arrhythmia (5) (6). However, almost two-thirds of patients with DCM do not have LGE, because the evaluation of LGE is a qualitative analysis of focal fibrosis, and diffuse myocardial fibrosis is difficult to detect as LGE. Recently, ECV measurement using T1 mapping on MRI has become available for the prediction of future MACE (7). MRI is sometimes contraindicated in cases with DCM because of the presence of mechanical devices or claustrophobia, and gadolinium contrast is also contraindicated in cases with renal dysfunction (9).

Increased ECV on LVM is almost equal to the higher amount of biopsy-proven myocardial fibrosis (16); accordingly, higher ECV means severe degeneration of LVM, which leads to lower LV function or ventricular arrhythmic events (8). The amount of myocardial fibrosis is a significant risk factor of future cardiac events in several myocardial diseases (5) (6) (8).

Additional radiation dose for late enhancement analysis on CT

Additional radiation dose is necessary for ECV analysis on CT but is a tradeoff for the important clinical information obtained. The effective dose for the late-phase scan in this study was 3.7±0.4 mSv, which is smaller than the effective dose for chest CT for evaluation of the lung (almost 5mSv) (17). The radiation dose for late phase cardiac images has recently decreased following the introduction of new iterative reconstruction techniques and wide coverage multi-detector CTs, and the image quality of late-phase cardiac images has improved (11). These changes have ameliorated the disadvantages of additional late phase cardiac imaging, and late phase cardiac scan should be recommended in cases with DCM.

Improvement in image quality of late enhancement

Contrast resolution of late phase cardiac images on CT is inferior to MRI, and MRI remains the gold standard modality for evaluation of myocardial damage on late phase images. Although CT attenuation value increases when a CT scan is performed using a lower tube voltage, image noise increases owing to the limited radiation dose (18). Recently, however, newer iterative reconstruction techniques have appeared, and the maximum tube current of CT scanners has increased. They help decrease image noise in images acquired using a lower tube voltage. We previously reported that the combination of new-generation CT and the iterative reconstruction technique is useful for improving the image quality of late enhancement on CT and higher diagnostic accuracy in the detection of myocardial fibrosis (12). Of note,

the improvement in image quality in late enhancement of LVM has resulted in the approval of ECV analysis using CT as a substitute for MRI in the latest guidelines for cardiac CT and cardiac amyloidosis from the Japanese Cardiovascular Society (19) (20).

Limitations

Several limitations of our study warrant mention. First, the study was conducted under a retrospective design at a single center. Second, ECV analysis was performed on single-energy images, and subtraction of late phase and non-contrast images was therefore necessary. Gaps between images in these 2 phases might cause under- or overestimation of ECV on single-energy images compared with analysis of dual-energy images using the latest CT scanners (without gaps). Finally, the study was conducted using different CT scanners, and difference between them may have affected the results.

Conclusion

Evaluation of ECV by CT is useful for the prediction of MACE in patients with DCM.

Declarations

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Data availability: Because of the sensitive nature of the data collected for this study, the data will not be made publicly available

Disclosure: All authors have no conflict of interest related to this article.

Ethical approval: The study was approved by the local Ethics Committee and Institutional Review Board and therefore conforms to all principles outlined in the 2nd Declaration of Helsinki.

Consent for publication: All authors have provided consent to publish the manuscript.

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Figures

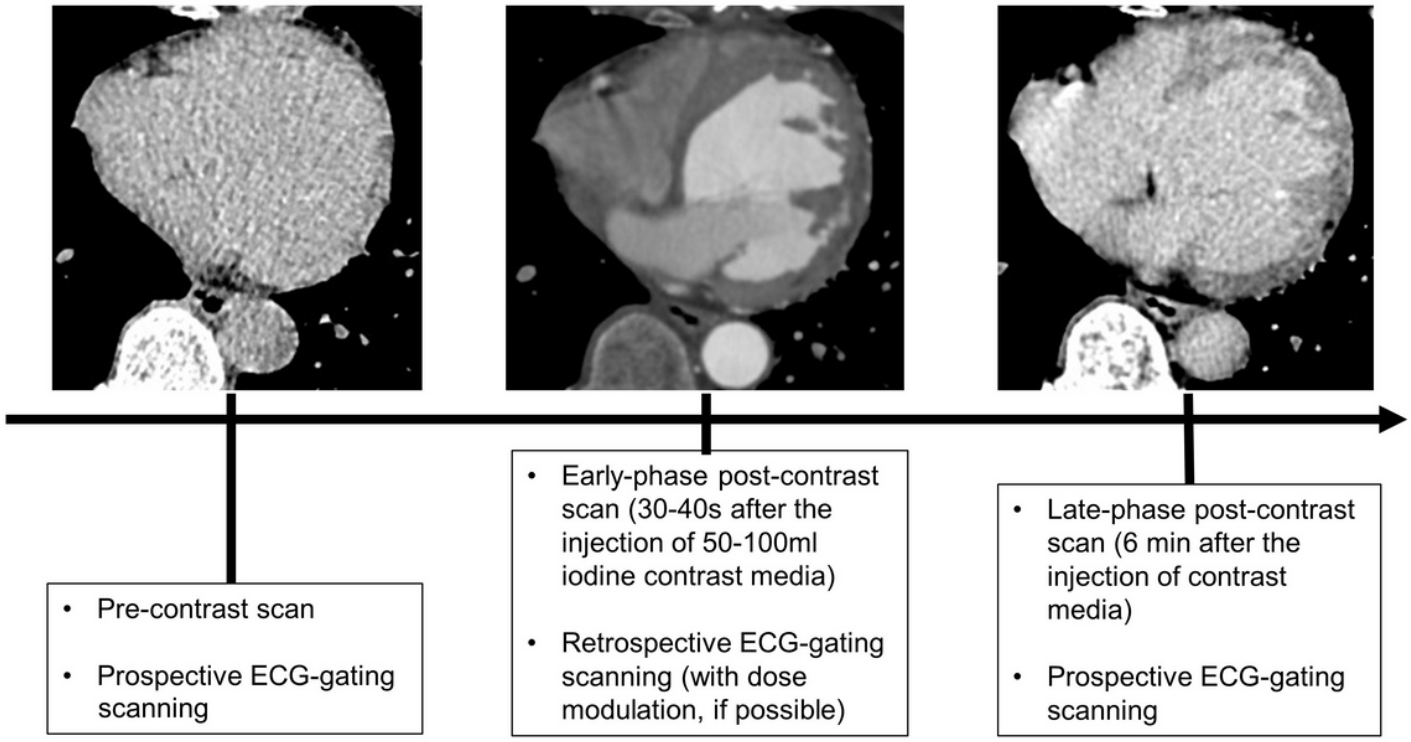

Figure 1

Details of the CT scan protocol

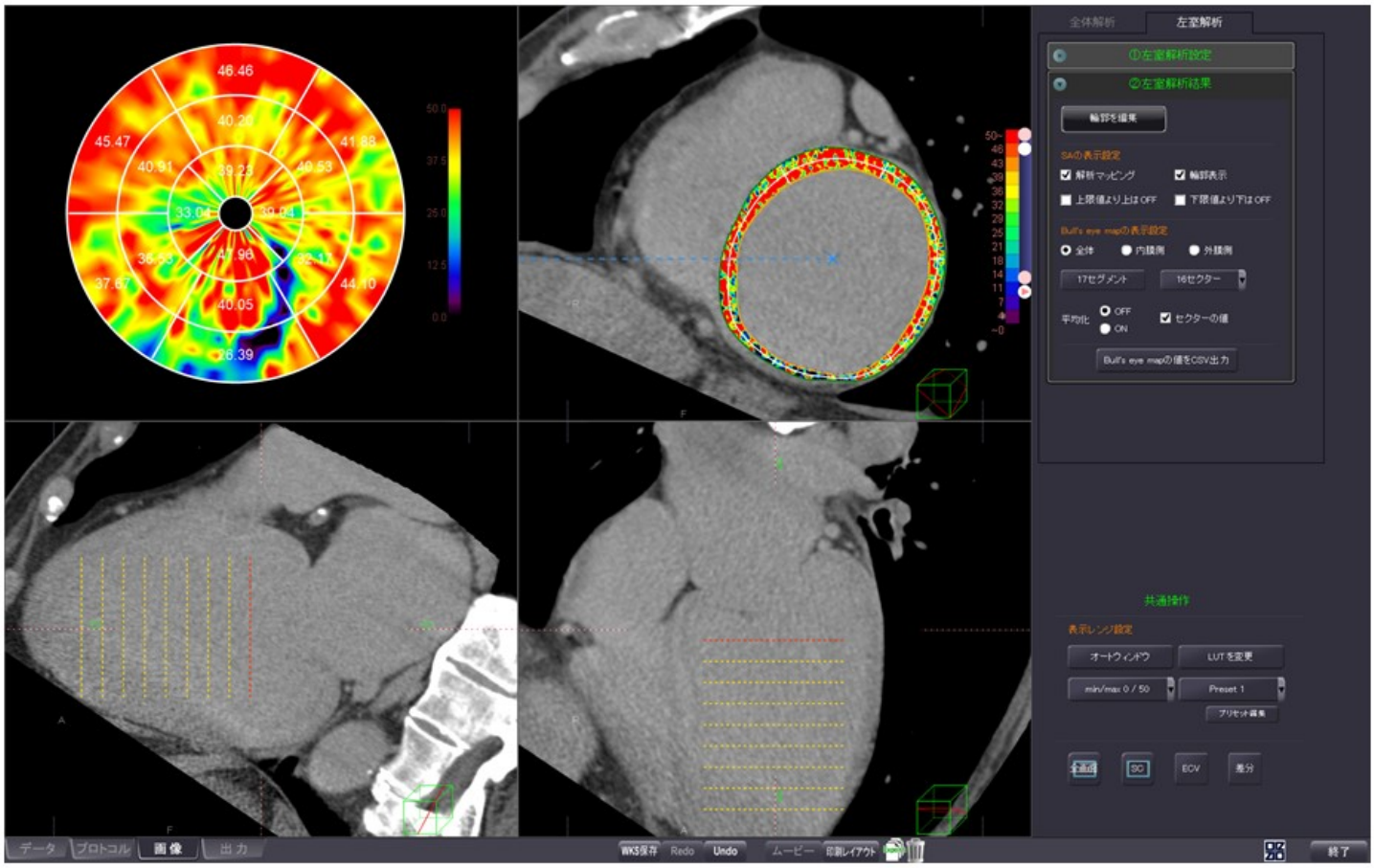

Figure 2

Details of ECV analysis on CT

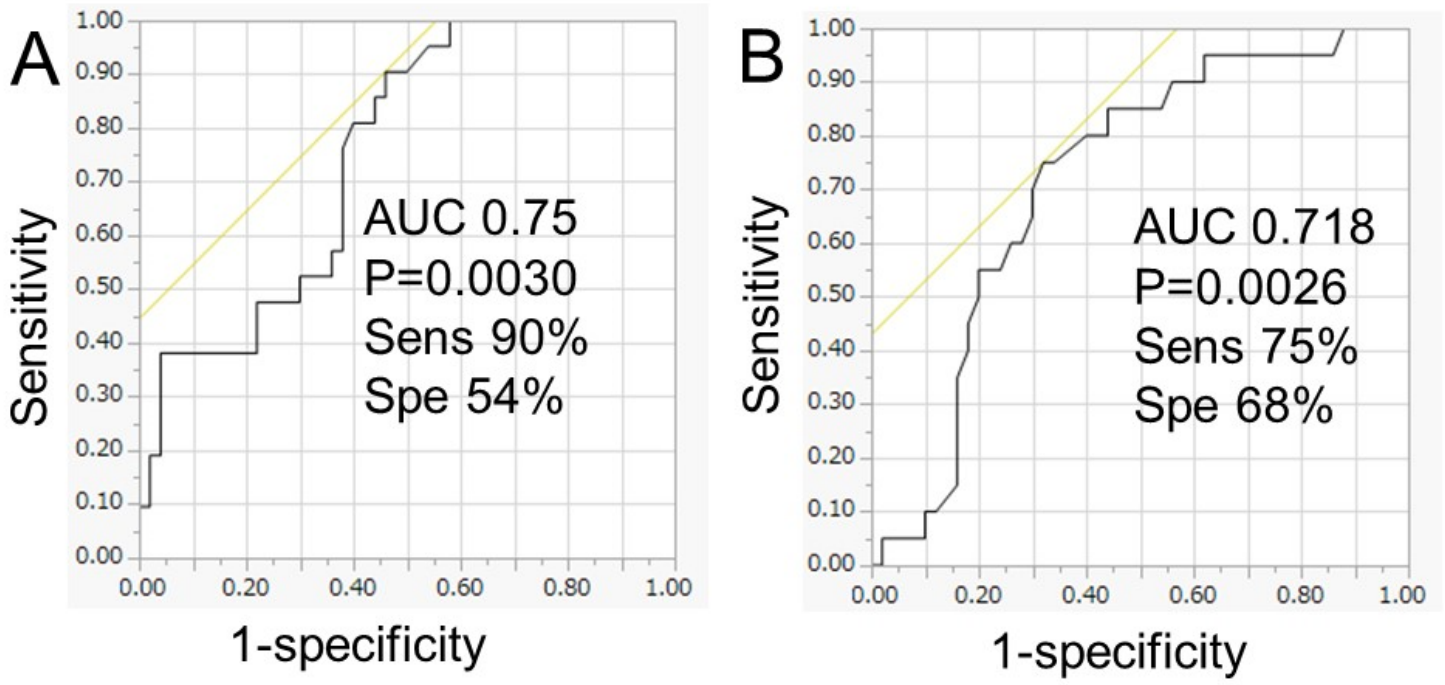

Figure 3

Receiver operating characteristics analysis for prediction of major adverse cardiac events The best cut-off value for extracellular volume fraction (ECV) on the left ventricular myocardium for prediction of major adverse cardiac events (MACE) was 32.7% based on receiver operating characteristics (ROC) analysis (A). The area under the curve of the receiver operating characteristics curve was 0.751 (P=0.0034) (A). The best cut-off value for left ventricular ejection fraction for prediction of MACE was 24% based on ROC analysis (B). The area under the curve of the receiver operating characteristics curve was 0.718 (P=0.0026) (B).

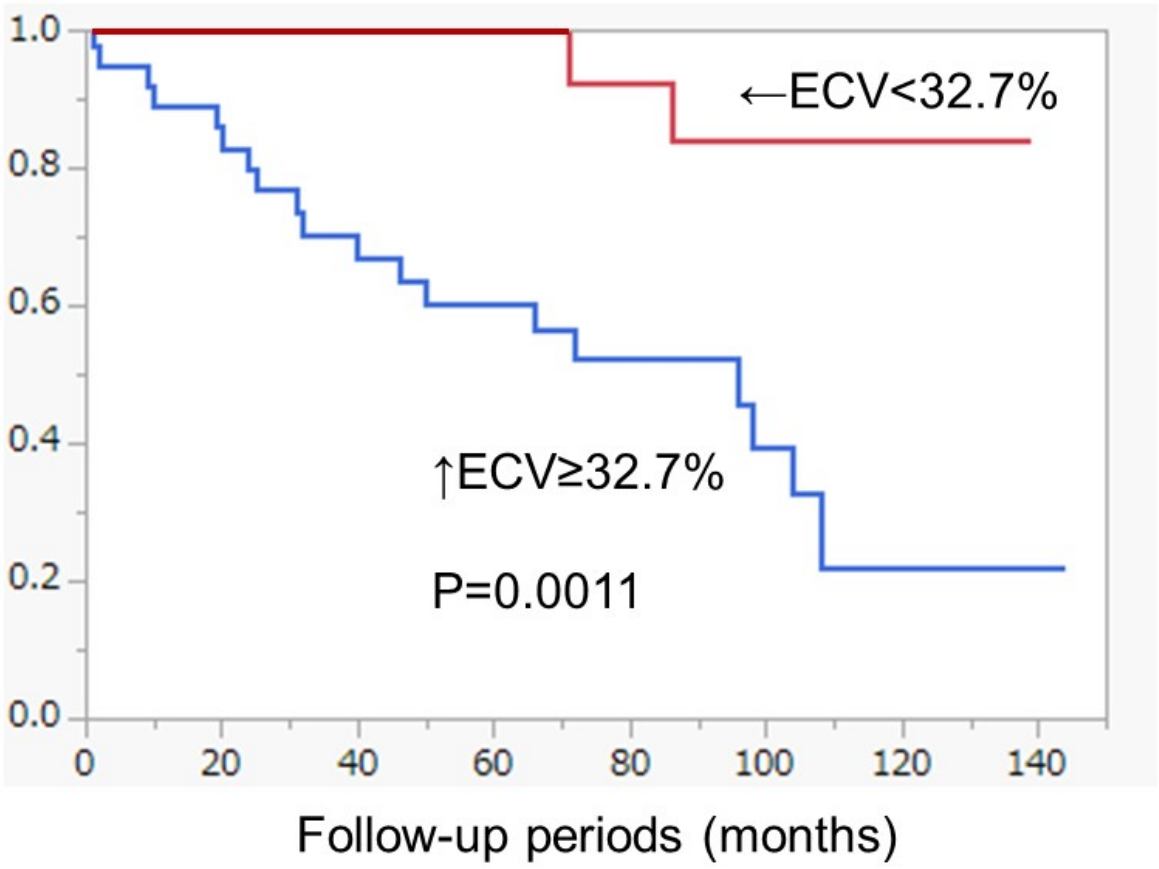

Figure 4

Incidence of major adverse cardiac events during follow-up by Kaplan-Meier analysis of cases with extracellular volume fraction ≥32.7% Cases with an extracellular volume fraction ≥32.7% had significantly higher major adverse cardiac events during the follow-up period based on the Kaplan-Meier analysis (P=0.0011).