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Noncontrast Myocardial T1 Mapping by Cardiac Magnetic Resonance Predicts Outcome in Patients With Aortic Stenosis

Heesun Lee, MD,[a,b] Jun-Bean Park, MD, PhD,[a,c] Yeonyee E. Yoon, MD,[a,d] Eun-Ah Park, MD, PhD,[e] Hyung-Kwan Kim, MD, PhD,[a,c] Whal Lee, MD, PhD,[e] Yong-Jin Kim, MD, PhD,[a,c] Goo-Yeong Cho, MD, PhD,[a,d] Dae-Won Sohn, MD, PhD,[a,c] Andreas Greiser, PhD,[f] Seung-Pyo Lee, MD, PhD[a,c]

ABSTRACT

OBJECTIVES The aim of this study was to evaluate whether native T1 value of the myocardium on cardiac magnetic resonance (CMR) could predict clinical events in patients with significant aortic stenosis (AS).

BACKGROUND Although previous studies have demonstrated the prognostic value of focal fibrosis using late gadolinium enhancement (LGE) by CMR in AS patients, the prognostic implication of diffuse myocardial fibrosis by noninvasive imaging remains unknown.

METHODS A prospective observational longitudinal study was performed in 127 consecutive patients with moderate or severe AS (68.8 ± 9.2 years of age, 49.6% male) and 33 age- and sex-matched controls who underwent 3-T CMR. The degree of diffuse myocardial fibrosis was assessed by noncontrast mapping of T1 relaxation time using modified Look-Locker inversion-recovery sequence, and the presence and extent of LGE were also evaluated. The AS patients were divided into 3 groups by the native T1 value. Primary endpoint was a composite of all-cause death and hospitalization for heart failure.

RESULTS Native T1 value was higher in AS patients, compared with control subjects (1,232 ± 53 ms vs. 1,185 ± 37 ms; $p = 0.008$). During follow-up (median 27.9 months), there were 24 clinical events including 9 deaths (6 pre-operative and 3 post-operative), the majority of which occurred in the patients in the highest T1 tertile group (2.4% vs. 11.6% vs. 42.9% for lowest, mid-, and highest tertile groups; $p < 0.001$ by log-rank test). The total number of events for both pre- and post-operative events also occurred more frequently in patients in the highest T1 tertile group. EuroSCORE II, the presence and/or extent of LGE, and the native T1 value were predictors of poor prognosis (adjusted hazard ratio for every 20-ms increase of native T1: 1.28; $p = 0.003$). In particular, the highest native T1 value provided further risk stratification regardless of the presence of LGE.

CONCLUSIONS High native T1 value on noncontrast T1 mapping CMR is a novel, independent predictor of adverse outcome in patients with significant AS. (J Am Coll Cardiol Img 2017;■:■-■) © 2017 by the American College of Cardiology Foundation.

From the [a]Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea; [b]Healthcare System Gangnam Center, Seoul National University Hospital, Seoul, Republic of Korea; [c]Cardiovascular Center, Seoul National University Hospital, Seoul, Republic of Korea; [d]Department of Cardiology, Cardiovascular Center, Seoul National University Bundang Hospital, Seongnam, Republic of Korea; [e]Department of Radiology, Seoul National University Hospital, Seoul, Republic of Korea; and [f]Siemens Healthcare, Erlangen, Germany. This study was supported by grants from the Korean Health Technology R&D Project (HI15C0399), Ministry of Health, Welfare & Family Affairs, and the Basic Science Research Program through the National Research Foundation of Korea (2014R1A1A1003004), Ministry of Education, South Korea. Other than financial support, the funders were not involved in protocol development or the study process, including implementation, management, data collection, or data analysis. Dr. Greiser is an employee of Siemens Healthcare. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis

AV = aortic valve

CMR = cardiac magnetic resonance

DMF = diffuse myocardial fibrosis

ECV = extracellular volume

HR = hazard ratio

LGE = late gadolinium enhancement

LV = left ventricle/ventricular

SAVR = surgical aortic valve replacement

TAVR = transcatheter aortic valve replacement

Myocardial fibrosis is a seminal pathological process that occurs in aortic stenosis (AS), one of the most common valvular diseases with high mortality (1,2). The chronic pressure overload to the left ventricle (LV) leads to degeneration of cardiomyocytes and to reactive fibrosis (2,3). The degree of myocardial fibrosis correlates with the degree of disease progression and predicts adverse clinical events in AS (4–6).

Although endomyocardial biopsy is the gold standard for detecting myocardial fibrosis (7), several practical limitations hinder its general utilization (8). Studies using cardiac magnetic resonance (CMR), from late gadolinium enhancement (LGE) to extracellular volume (ECV) calculation, have demonstrated the noninvasive detection of myocardial fibrosis (4–7,9–11). However, LGE needs gadolinium-based contrast and can image only focal myocardial scar, whereas diffuse myocardial fibrosis (DMF) ensues following pressure overload to the LV (6–9). Measurement of ECV using post-contrast T1 is helpful for quantification of the degree of DMF, but also uses contrast and requires additional time to achieve equilibrium between the blood and the myocardium (10,11). Furthermore, not much is known about the prognostic implication of quantifying DMF with noninvasive imaging.

The 3-T magnetic resonance allows better tissue characterization than 1.5-T by improving the signal-to-noise ratio with the upgraded bulk magnetization and suppressing background noise from the lengthening of T1 relaxation time. This enables better discrimination of fibrosis from normal myocardium without contrast (12). We and others have demonstrated that native T1 relaxation time may help in estimating the degree of DMF in AS patients (13,14). In the present study, we hypothesized that assessment of the degree of DMF using the native T1 value on CMR would be helpful to predict the prognosis of patients with significant AS.

METHODS

The detailed methods are described in a separate file (Online Appendix).

STUDY DESIGN AND POPULATION. Between 2011 and 2015, we consecutively enrolled patients with moderate or severe AS for this prospective study. The local Institutional Review Board approved the protocol, and patients gave written informed consent. Significant AS of moderate or severe degree was defined by echocardiography as transaortic peak velocity ≥3.0 m/s or transaortic mean pressure gradient ≥20 mm Hg (15). After excluding patients with ≥moderate degree of other valvular disease, other medical condition with life expectancy <1 year, uninterpretable images, and those lost to follow-up, 127 patients remained for the final analysis (**Figure 1**), 87 patients of which underwent aortic valve (AV) replacement regardless of the native T1 value. The patients were divided into 3 subgroups of equal numbers according to the native T1 values. Healthy volunteers of similar age and sex distribution (n = 33) with no cardiovascular risk factors were enrolled as control subjects (16).

CMR IMAGING WITH NONCONTRAST T1 MAPPING. All subjects underwent CMR imaging on a 3-T scanner (Magnetom Trio, Siemens Healthcare, Erlangen, Germany) with a 6-channel phased array and spine coils (17). A prototype modified Look-Locker inversion-recovery sequence (18) was used for noncontrast mapping of myocardial T1 relaxation time at the mid-ventricular short-axis sections of the papillary muscle level before administration of the gadolinium contrast, the protocol of which was previously described (13). Briefly, 3 images were gained in the first and second Look-Locker segments and 5 in the third segment, thus, a total of 11 images from 17 heartbeats were prepared. The native T1 value was measured by drawing the region of interests manually on the septal segment of the mid-ventricular slice, excluding the myocardium with LGE (13,14,19). Approximately 10 min after gadolinium-based contrast injection, phase-sensitive inversion recovery sequence was applied to image the LGE on long- and short-axis images. The region of LGE was depicted semiautomatically as the pixels of myocardium with signal intensity >5 SD of the remote normal myocardium using an adequate software (CVI 42 version 5.0, Circle Cardiovascular Imaging, Calgary, Alberta, Canada) (20). The extent of LGE was expressed as the percentage of total LV mass.

FOLLOW-UP. The primary outcome was a composite of all-cause death and unexpected hospitalization for heart failure. The cause of death was further classified as cardiovascular and noncardiovascular origins as needed. Unplanned hospitalization for heart failure was defined as admission to the hospital with signs and symptoms of decompensated heart failure requiring intravenous medications. The decision of surgical aortic valve replacement (SAVR) and transcatheter aortic valve replacement (TAVR) was made without the native T1 value information, by the duty physician's discretion.

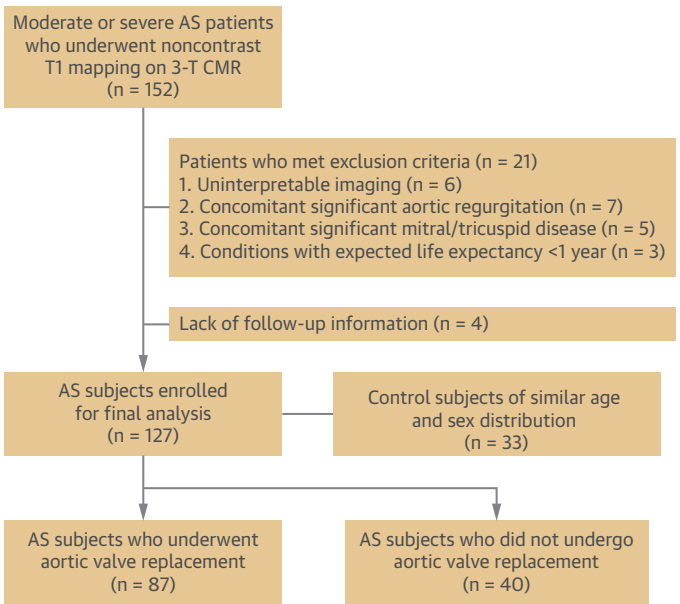
STATISTICAL ANALYSIS. Baseline clinical and imaging characteristics were compared between the AS patients and the control subjects, and between the 3 AS subgroups according to the native T1 tertiles using either the Student *t* test, analysis of variance, or chi-square test as appropriate. Survivals according to the native T1 tertiles were determined by Kaplan-Meier analysis and compared with the log-rank test. Univariate and multivariate Cox regression analysis was used to estimate the risk of clinical events and to seek for independent predictors in order. The covariates used in the multivariate Cox regression analysis were chosen carefully to avoid overfitting according to the clinical relevance (21). The risk of clinical events was expressed as hazard ratio (HR) and corresponding 95% confidence interval. The receiver-operating characteristic analysis was performed with the indexed AV area, the EuroSCORE II, the presence of LGE, and the native T1 value, and the area under the curve for the prediction of further clinical events was analyzed to evaluate the prognostic value of combining each parameter. The discriminative power of adding native T1 value on top of the indexed AV area, the EuroSCORE II, and the presence of LGE was compared using a previous method by DeLong et al. (22). A p value <0.05 was considered statistically significant.

RESULTS

BASELINE CHARACTERISTICS OF THE STUDY PARTICIPANTS. The AS patients (n = 127; mean age 68.8 years; male 49.6%) were compared with the 33 healthy control subjects. The mean native T1 value of the AS group was significantly higher than that of the control subjects (1,232 ± 53 ms vs. 1,185 ± 37 ms; p = 0.008). The cutoff native T1 values for the 3 AS subgroups were 1,200 ms and 1,250 ms, respectively (**Figure 2**). Between the 3 AS subgroups by the native T1 value, patients with a higher T1 value were more likely to be male, have a higher EuroSCORE II, have a history of prior coronary revascularization, and be more frequently symptomatic. The LV volumes tended to be larger, and the LV ejection fraction smaller, with increasing native T1 values. There was a trend toward increasing extent of LGE in the AS patients with a higher native T1 value (2.1 ± 1.1% vs. 5.4 ± 5.3% vs. 8.1 ± 5.9%; p = 0.061) (**Table 1**).

Intraobserver and interobserver variability was good for the native T1 values (3.7% for intraobserver variability, 4.1% for interobserver variability). The corresponding intraclass correlation coefficients for intraobserver and interobserver variability were 0.97 and 0.96, respectively ($p < 0.001$ for both).

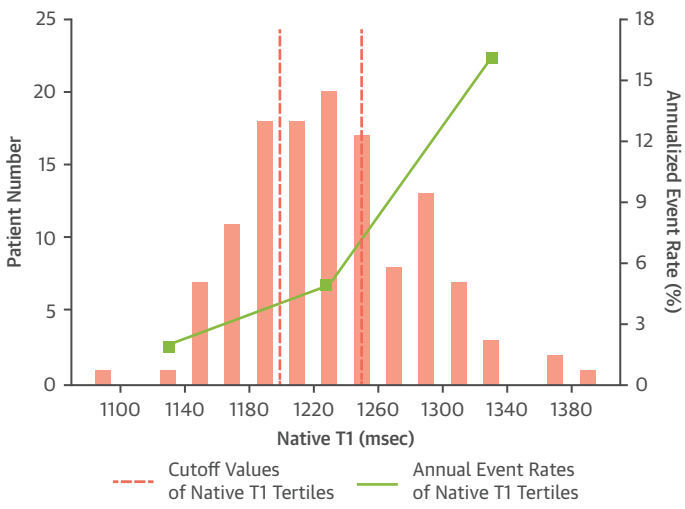
FIGURE 1 Flowchart of Study Participants



AS = aortic stenosis; CMR = cardiac magnetic resonance.

OVERALL PRIMARY ENDPOINT OF PATIENTS ACCORDING TO THE NATIVE T1 VALUES. During a median follow-up duration of 27.9 months (interquartile range: 16.4 to 36.5 months), 24 clinical events (cumulative event rate 18.9%) occurred, 9 all-cause

FIGURE 2 Distribution Pattern of the Native T1 Value in the AS Patients and Its Relationship With the Clinical Events



The native T1 values of significant AS patients were normally distributed, and the clinical events tended to occur more frequently in patients with higher native T1 values.
AS = aortic stenosis.

TABLE 1 Clinical and Imaging Characteristics According to Study Group and Native Myocardial T1 Tertile Category

	Healthy Volunteers (n = 33)	AS Subjects (n = 127)	p Value	Lowest T1 Tertile (n = 42)	Mid T1 Tertile (n = 43)	Highest T1 Tertile (n = 42)	p Value
Clinical parameters							
Age, yrs	68.8 ± 4.4	68.8 ± 9.2	0.886	67.4 ± 10.5	69.9 ± 7.9	69.0 ± 9.1	0.455
Male	16 (48.4)	63 (49.6)	0.671	15 (35.7)	21 (48.8)	27 (64.3)	0.032
Body surface area, m^2	1.65 ± 0.13	1.67 ± 0.15	0.427	1.65 ± 0.16	1.67 ± 0.16	1.69 ± 0.13	0.491
Smoking		29 (22.8)		7 (16.7)	13 (30.2)	9 (21.4)	0.318
Hypertension		84 (66.1)		26 (61.9)	29 (67.4)	29 (69.0)	0.768
Diabetes mellitus		34 (26.8)		10 (23.8)	14 (32.6)	10 (23.8)	0.574
Hyperlipidemia		36 (28.3)		9 (21.4)	13 (30.2)	14 (33.3)	0.454
Atrial fibrillation		15 (11.8)		4 (9.5)	4 (9.3)	7 (16.7)	0.491
Prior coronary revascularization		17 (13.4)		2 (4.8)	5 (11.6)	10 (23.8)	0.034
EuroSCORE II, %		1.58 ± 0.99		1.24 ± 0.68	1.65 ± 0.83	1.86 ± 1.28	0.013
Hemodynamics							
Systolic blood pressure, mm Hg	120.5 ± 13.5	130.2 ± 18.9	0.030	131.8 ± 17.1	129.4 ± 21.8	129.5 ± 17.8	0.812
Diastolic blood pressure, mm Hg	67.8 ± 10.2	70.9 ± 10.8	0.318	71.8 ± 9.6	69.2 ± 12.1	71.6 ± 10.5	0.464
Heart rate, beats/min	65.9 ± 8.1	66.6 ± 12.4	0.686	66.2 ± 11.6	67.1 ± 13.1	66.6 ± 12.7	0.956
Symptoms							
Any of typical AS symptoms		68 (54.5)		15 (35.7)	25 (59.5)	28 (65.1)	0.029
Dyspnea, NYHA functional class II–IV		62 (48.8)		15 (35.7)	25 (58.1)	22 (52.4)	0.128
Chest pain		33 (26.0)		7 (16.7)	14 (32.6)	12 (28.6)	0.215
Syncope or pre-syncope		16 (12.6)		4 (9.5)	2 (4.7)	10 (23.8)	0.022
Medications							
RAS blocker		62 (48.8)		20 (47.6)	22 (51.2)	20 (47.6)	0.931
Beta-blocker		43 (33.9)		12 (28.6)	17 (39.5)	14 (33.3)	0.563
Calcium-channel blocker		31 (24.4)		10 (23.8)	13 (30.2)	8 (19.0)	0.484
Diuretics		33 (26.0)		7 (16.7)	11 (25.6)	15 (35.7)	0.138
Echocardiography							
LV end-diastolic diameter, mm	46.1 ± 3.8	49.7 ± 6.3	0.006	46.6 ± 4.5	50.6 ± 6.6	51.8 ± 6.5	<0.001
LV end-systolic diameter, mm	28.6 ± 3.1	31.4 ± 7.4	0.013	28.0 ± 2.9	32.2 ± 8.2	34.3 ± 8.4	<0.001
Interventricular septal thickness, mm	9.0 ± 1.3	11.3 ± 2.1	<0.001	10.9 ± 1.9	11.4 ± 1.8	11.5 ± 2.6	0.459
Posterior wall thickness, mm	9.0 ± 1.1	11.0 ± 2.0	<0.001	10.3 ± 1.8	11.4 ± 1.7	11.3 ± 2.2	0.018
LVEF, %	61.6 ± 10.0	60.1 ± 9.7	0.300	64.0 ± 4.5	59.4 ± 11.3	57.0 ± 10.6	0.003
LA diameter, mm	38.1 ± 6.0	44.3 ± 6.8	0.002	42.7 ± 5.7	44.4 ± 6.6	45.8 ± 7.8	0.114
E velocity, m/s	0.55 ± 0.13	0.71 ± 0.26	<0.001	0.67 ± 0.24	0.73 ± 0.28	0.73 ± 0.27	0.456
e′ velocity at septal annulus, cm/s	6.1 ± 1.6	4.4 ± 1.4	0.002	4.3 ± 1.3	4.4 ± 1.4	4.3 ± 1.4	0.912
E/e′	9.6 ± 2.9	17.6 ± 8.4	<0.001	16.3 ± 6.2	17.8 ± 9.7	18.6 ± 8.9	0.463
Transaortic peak velocity, m/s		4.4 ± 0.8		4.3 ± 0.9	4.5 ± 0.8	4.6 ± 0.9	0.228
Transaortic mean PG, mm Hg		48.0 ± 19.3		42.4 ± 17.8	49.4 ± 18.4	52.0 ± 20.7	0.064
AV area, cm^2		0.82 ± 0.25		0.89 ± 0.24	0.82 ± 0.27	0.74 ± 0.21	0.021
Severe AS*		79 (62.2)		21 (50.0)	27 (62.8)	31 (73.8)	0.079
CMR							
LV end-diastolic volume, ml/m^2	76.9 ± 10.2	99.1 ± 34.5	<0.001	84.1 ± 22.8	103.6 ± 35.5	109.6 ± 38.5	0.002
LV end-systolic volume, ml/m^2	27.9 ± 7.0	41.6 ± 30.2	<0.001	27.3 ± 11.9	45.6 ± 32.1	51.8 ± 35.8	<0.001
LVEF, %	63.8 ± 7.2	61.8 ± 14.1	0.003	68.8 ± 8.0	60.6 ± 13.9	56.0 ± 16.2	<0.001
LV mass index, g/m^2	55.7 ± 96.5	96.5 ± 35.5	<0.001	84.5 ± 24.7	95.5 ± 32.2	109.4 ± 43.5	<0.001
Presence of LGE	0 (0.0)	41 (32.3)	<0.001	10 (23.8)	13 (30.2)	18 (42.9)	0.164
% LGE mass		5.2 ± 4.8		2.1 ± 1.1	5.4 ± 5.3	8.1 ± 5.9	0.061
Native myocardial T1 value, ms	1,185 ± 37	1,232 ± 53	0.008	1,176 ± 23	1,229 ± 14	1,290 ± 33	–

Values are mean ± SD or n (%). *Severe AS was defined as transaortic peak velocity ≥4.0 m/s, transaortic mean pressure gradient ≥40 mm Hg, or aortic valve area calculated using the continuity equation ≤1.0 cm^2 on echocardiography.

AS = aortic stenosis; AV = aortic valve; CMR = cardiac magnetic resonance; E = early diastolic transmitral flow velocity; e′ = early diastolic mitral annular velocity; EF = ejection fraction; LA = left atrium; LGE = late gadolinium enhancement; LV = left ventricle; NYHA = New York Heart Association functional class; PG = pressure gradient; RAS = renin-angiotensin system.

deaths and 15 hospitalizations for heart failure (Table 2). Seven of the deaths (77.8%) were from cardiovascular causes (4 acute heart failure, 2 cardiogenic shock, and 1 ischemic stroke), and 2 deaths were attributed to sepsis and lung cancer, respectively.

When stratified by the native T1 tertiles, the overall clinical events tended to occur more frequently in the

AS patients with higher native T1 value (Figure 2). Additionally, each component of the endpoint significantly increased with increasing native T1 tertiles (death 0.0% vs. 2.3% vs. 19.0%, p = 0.001; hospitalization for heart failure 2.4% vs. 9.3% vs. 23.8%, p = 0.008) (Table 2). Kaplan-Meier survival curves demonstrated that the AS patients in the highest native T1 tertile had the worst event-free survival (p < 0.001 by log-rank test) (Figure 3A). The representative images of noncontrast T1 mapping results along with the clinical events are shown (Figure 4).

TEMPORAL RELATIONSHIP BETWEEN AV REPLACEMENT AND CLINICAL EVENTS. Eighty-seven patients underwent AV replacement (68.5%): 70 SAVR and 17 TAVR. When the events were divided in temporal relation to the AV replacement, the primary composite endpoint that occurred before operation tended to be significantly frequent in the highest T1 tertile group (p = 0.002 by log-rank test) (Figure 3B). Again, each component of the endpoint significantly increased with increasing native T1 tertiles (death 0.0% vs. 2.3% vs. 11.9%, p = 0.010; hospitalization for heart failure 2.4% vs. 9.3% vs. 21.5%, p = 0.006) (Table 2). All of the pre-operative deaths were of cardiovascular cause, except for 1 death that resulted from lung cancer in the mid-T1 tertile group.

Among the 87 patients who underwent AV replacement, 72 patients (82.8%) had severe and 15 (17.2%) had moderate AS. The most common indication for AV replacement in moderate AS was concomitant coronary artery bypass surgery. All patients underwent CMR before AV replacement, and the decision of the operation or the procedure was made irrespective of the native T1 values. The primary composite endpoint after the AV replacement occurred in 4 patients (3 cases of all-cause death and 1 case of hospitalization for heart failure), all of which occurred exclusively in the highest T1 tertile group (p = 0.024 by log-rank test) (Table 2, Figure 3C).

NATIVE T1 VALUE AS AN INDEPENDENT PROGNOSTIC FACTOR. Among the clinical parameters, a history of diabetes mellitus or prior coronary revascularization, higher EuroSCORE II, and prior use of diuretics were univariate predictors of clinical events (Table 3). Among the imaging parameters, native T1 value was a significant predictor of clinical events (unadjusted HR: 6.34, p < 0.001 for the highest native T1 tertile; unadjusted HR: 1.27, p < 0.001 for every 20-ms increase of native T1), as well as the LGE (unadjusted HR: 2.81, p = 0.022 for the presence of LGE; unadjusted HR: 1.15, p = 0.047 for every 1% increase of LGE mass). To avoid overfitting (21), we included only EuroSCORE II, prior use of diuretics, the presence or extent of LGE, and native T1 in the multivariate analysis. All of these parameters remained as independent predictors of clinical events, except for the use of diuretics. Notably, the highest native T1 tertile or native T1 value itself was a robust predictor of worse outcome (adjusted HR: 4.45, p = 0.006 for the highest native T1 tertile; adjusted HR: 1.28, p = 0.003 for every 20-ms increase of native T1). The highest native T1 tertile was able to stratify both groups of AS patients, with or without LGE on CMR (Figure 5) and the addition of native T1 tertile on top of a model comprising indexed AV area, EuroSCORE II, and the presence of LGE provided further risk stratification (Figure 6).

TABLE 2 Clinical Events of Study Participants According to Native Myocardial T1 Tertile Category

	Entire Participants	Lowest T1 Tertile	Mid T1 Tertile	Highest T1 Tertile	p Value
Total clinical events	127	42	43	42	
Clinical event	24 (18.9)	1 (2.4)	5 (11.6)	18 (42.9)	<0.001
Death	9 (7.1)	0 (0.0)	1 (2.3)	8 (19.0)	0.001
Hospitalization for heart failure	15 (11.8)	1 (2.4)	4 (9.3)	10 (23.8)	0.008
Pre-operative clinical events	127	42	43	42	
Clinical event	20 (15.7)	1 (2.4)	5 (11.6)	14 (33.3)	<0.001
Death	6 (4.7)	0 (0.0)	1 (2.3)	5 (11.9)	0.010
Hospitalization for heart failure	14 (11.0)	1 (2.4)	4 (9.3)	9 (21.4)	0.006
Post-operative clinical events	87	22	32	33	
Clinical event	4 (4.6)	0 (0.0)	0 (0.0)	4 (12.1)	0.023
Death	3 (3.4)	0 (0.0)	0 (0.0)	3 (9.1)	0.051
Hospitalization for heart failure	1 (1.1)	0 (0.0)	0 (0.0)	1 (3.0)	0.266

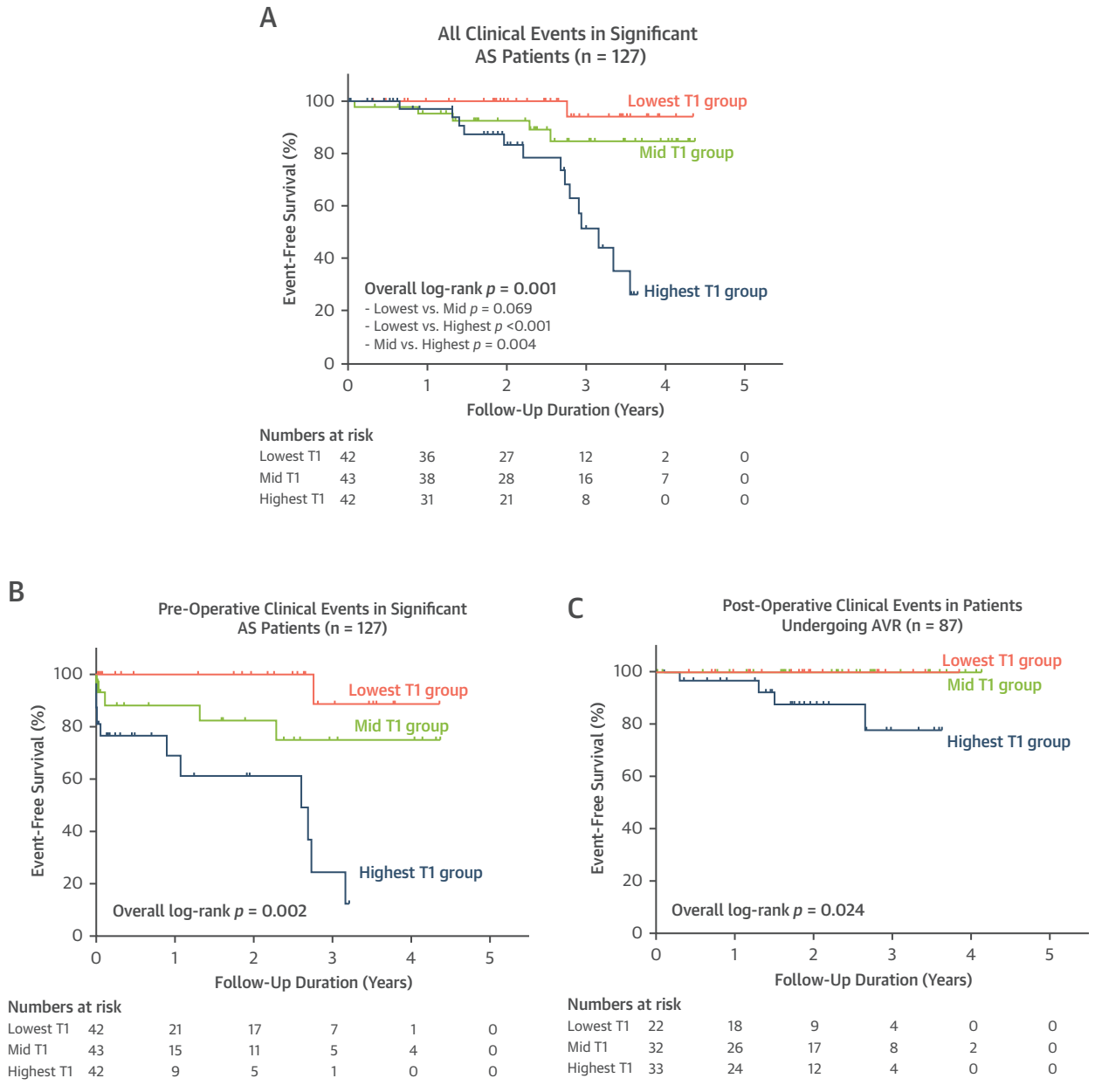
Values are n or n (%).

DISCUSSION

The main findings of the present study are: 1) noninvasive measurement of DMF by native T1 values on noncontrast T1 mapping CMR correlates well with other parameters, implying disease progression in AS; 2) a high native T1 value identifies patients at high risk of clinical events both pre- and post-operatively; and 3) the native T1 value is an independent predictor of outcome, in addition to other prognosticators such as EuroSCORE II or LGE on CMR. Altogether, this prospective study evaluated the clinical implication of the native T1 value in patients with significant AS and suggests that the noninvasive assessment of DMF without contrast may potentially be helpful for clinical decision making in AS.

ASSESSMENT OF DMF BY NONCONTRAST T1 MAPPING IN AS. Although previous studies have demonstrated that noninvasive measures of myocardial fibrosis are

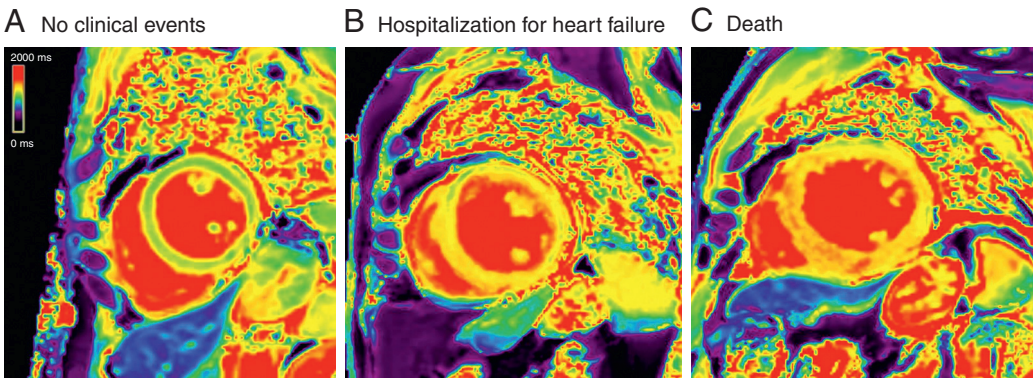
FIGURE 3 Overall Event-Free Survival According to the Tertiles of Native T1 Values



The patients in the highest T1 tertile subgroup had the worst overall clinical outcome: **(A)** during the entire follow-up (n = 127); **(B)** before aortic valve replacement (AVR) (n = 127); and **(C)** after AVR (n = 87). The x-axis is the time from enrollment in **A and B,** and the time from operation in **C**. The patients who underwent AVR were considered as censored after the operation in **B**. AS = aortic stenosis.

significantly associated with poor prognosis in AS patients, these are mainly focused on detection of LGE by CMR, standing for "focal" myocardial scar (5,6,9). The sensitivity of LGE-CMR is limited for absolute quantification of DMF, because the mechanism of LGE involves the nulling of the "normal" myocardium. In the setting of DMF, the nulling is questionable because of no evidence of normal myocardium (7,8), and myocardial fibrosis occurs in a diffuse manner following AS. Additionally, DMF is an early phenomenon preceding focal scarring, and therefore noninvasive assessment of DMF may enable early detection of, and possibly, reversal of the disease under appropriate management (23,24).

FIGURE 4 Representative T1 Mapping Images of Patients



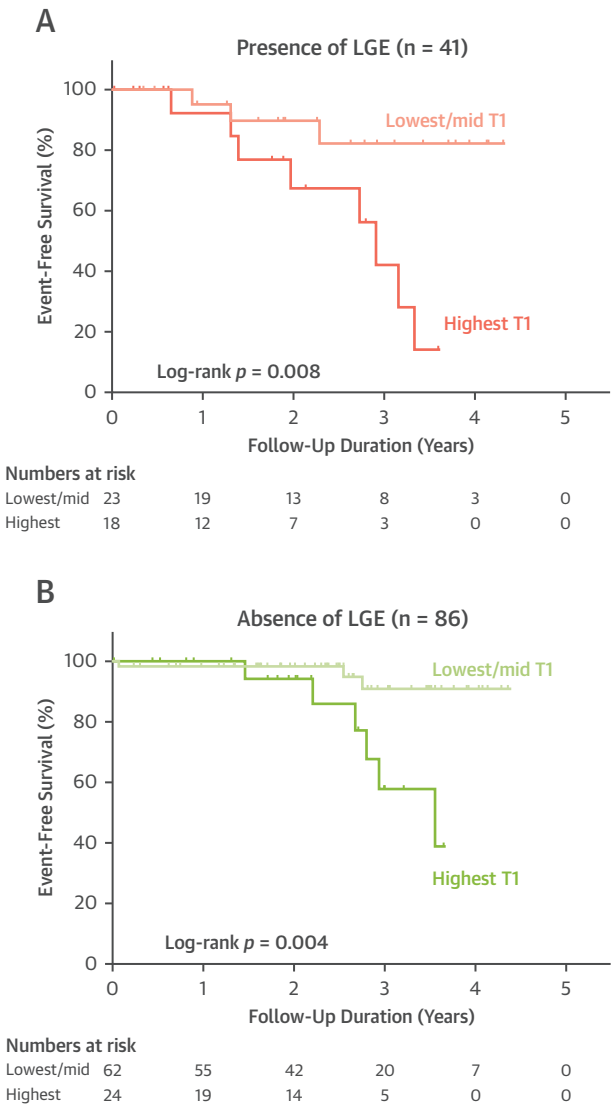
(A) A 63-year-old woman with moderate aortic stenosis (AS) who did not experience any clinical event. The native T1 value was 1,163 ms. **(B)** A 70-year-old man with severe AS who was hospitalized for decompensated heart failure. The native T1 value was 1,257 ms. **(C)** A 65-year-old man with severe AS who died during follow-up. The native T1 value was 1,385 ms.

TABLE 3 Univariate and Multivariate Analysis of Clinical Events

	Unadjusted HR (95% CI)	p Value	Adjusted HR* (95% CI)	p Value	Adjusted HR† (95% CI)	p Value
Clinical parameters						
Age, yrs	1.21 (0.50–2.92)	0.675				
Male	1.49 (0.61–3.63)	0.387				
Smoking	0.86 (0.29–2.57)	0.785				
Hypertension	2.74 (0.80–9.36)	0.108				
Diabetes mellitus	2.64 (1.09–6.41)	0.032				
Hyperlipidemia	2.06 (0.85–4.98)	0.108				
Atrial fibrillation	1.59 (0.53–4.78)	0.406				
Prior coronary revascularization	3.35 (1.29–8.75)	0.013				
EuroSCORE II	1.74 (1.36–2.24)	<0.001	1.39 (1.07–2.00)	0.042	1.50 (1.09–2.07)	0.013
Systolic blood pressure ≥140 mm Hg	1.40 (0.57–3.44)	0.459				
Any of typical AS symptoms	3.21 (0.94–13.83)	0.078				
Dyspnea, NYHA functional class II–IV	1.60 (0.85–3.91)	0.107				
Chest pain	1.21 (0.46–3.15)	0.698				
Syncope/pre-syncope	1.40 (0.41–4.80)	0.590				
RAS blocker	1.61 (0.66–3.96)	0.295				
Beta-blocker	0.54 (0.20–1.49)	0.233				
Calcium-channel blocker	2.49 (0.97–6.42)	0.059				
Diuretics	2.61 (1.08–6.32)	0.033	1.94 (0.94–2.92)	0.074	1.91 (0.92–2.81)	0.107
AV replacement	1.03 (0.39–2.67)	0.960				
Imaging parameters						
Indexed AV area on echocardiography	1.52 (0.21–11.13)	0.646				
LVEF on echocardiography, per 5% decrement	1.38 (0.96–4.17)	0.085				
Severe AS on echocardiography	1.68 (0.65–4.39)	0.286				
LVEF on CMR, per 5% decrement	1.76 (0.97–4.33)	0.069				
Indexed LV mass on CMR, per 10-g/m^2 increment	1.02 (0.95–1.15)	0.093				
Presence of LGE*	2.81 (1.17–6.80)	0.022	1.56 (1.05–4.37)	0.042		
% LGE mass, per 1% increment†	1.15 (1.01–1.38)	0.047			1.19 (1.07–1.90)	0.032
Highest native myocardial T1 tertile*	6.34 (2.43–16.56)	<0.001	4.45 (1.52–12.95)	0.006		
Native myocardial T1, per 20-ms increment†	1.27 (1.19–1.34)	<0.001			1.28 (1.10–1.46)	0.003

*Multivariate models for categorical variables of CMR. †Multivariate models for continuous variables of CMR.
CI = confidence interval; HR = hazard ratio; other abbreviations as Table 1.

FIGURE 5 Overall Event-Free Survival According to the Tertiles of Native T1 Values in Patients With or Without LGE



The highest native T1 tertile group is predictive of future clinical events in both groups of AS patients: **(A)** with LGE and **(B)** without LGE. AS = aortic stenosis; LGE = late gadolinium enhancement.

There have been various efforts to develop imaging methods for evaluating DMF (10–13), and several investigators including ours have demonstrated that by using T1 mapping, DMF may be quantified without contrast (12,13,25–27). In the present study involving one of the largest populations of AS patients with noncontrast T1 mapping, patients with significant AS had notably higher native T1 values than normal subjects by an average difference of approximately 50 ms, similar to the results of other studies for assessing DMF by noncontrast T1 mapping on 3-T CMR (12,13). Also, LGE was detected more frequently with the increase of native T1 value, as well as significant changes in the parameters implicating disease progression, such as increase in LV or left atrial dimensions and decrease in AV area. These findings indicate that native T1 value may be a good surrogate marker of early detection and severity of disease in AS.

The improved contrast of noncontrast T1 mapping following the introduction of 3-T CMR allows more accurate tissue discrimination (27). Also, noncontrast T1 mapping does not need gadolinium-based contrast, which is contraindicated in chronic kidney disease patients, a condition frequently encountered in AS patients (28). The reproducibility of native T1 has been reported to be comparable to ECV in AS patients (29). Altogether, native T1 value on noncontrast T1 mapping CMR can be a simple, but promising, tool for assessing DMF in AS.

PROGNOSTIC VALUE OF NATIVE T1 VALUE IN AS. High native T1 has been shown to be a strong predictor of adverse outcomes in other cardiac conditions where DMF develops with disease progression (12,30–32), whereas evidence supporting its clinical benefit in valvular heart disease remains scarce. The most important finding of this study is that native T1 value is a powerful predictor of adverse clinical events in AS. There was only 1 admission for decompensated heart failure in the patients with the lowest T1 tertile, which was fully recovered after treatment. Conversely, 19% of patients with the highest native T1 had died, and 24% had experienced hospitalization for heart failure, with events occurring throughout the whole follow-up period and both before and after AV replacement. Considering that the entire study population consisted of subjects with moderate or severe AS regardless of symptoms or operation, our results may be applied to a more generalized AS population than previous studies (13,33). Regardless of the presence of LGE, a predictor that recent prior studies had verified (5,6,9), the highest native T1 value could provide incremental prognostic utility in AS patients.

Remarkably, in the subgroup analysis of events that occurred before operation, 3 of 6 patients who died before AV replacement had moderate AS and were in the highest native T1 tertile group. All deaths were of cardiovascular cause. These patients would not be considered as candidates for AV replacement under the current guidelines (15), and this suggests native T1 as an indication for early surgery. Some clinicians advocate early surgery in severe but asymptomatic AS patients (22,34). However, prior

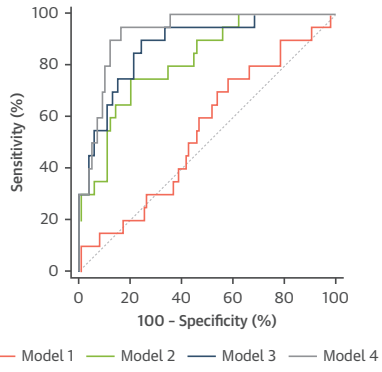
studies have demonstrated a fairly wide distribution of the degree of DMF in these asymptomatic patients, questioning the possibility of unnecessary surgery (13,35). Combining previous results with ours suggests that an integrated approach using novel noninvasive measures of DMF, such as high native T1 value, may perform better in identifying high-risk patients who might benefit from early AV replacement or meticulous surveillance.

STUDY LIMITATIONS. First, the event rate of the current study population was lower than that of others (4,5). This may reflect the ethnic difference in the study participants and the possibility that asymptomatic patients might have undergone AV replacement. However, the decision of radical treatment for AS was made independent of the CMR results, and the significant association of the native T1 value with adverse outcome in patients who underwent SAVR or TAVR supports that our analysis results may not be a result of selection bias. Further, the statistical power of our study was estimated to be 91.3% in the multivariate Cox regression model, which is sufficient enough to accept the null hypothesis at a type I error rate of 5% (36,37). Second, several known risk factors of outcome such as symptoms, age, and LV systolic function were not predictive of mortality. However, our study population was a heterogeneous mixture of moderate or severe degree and symptomatic or asymptomatic patients. Some parameters reached borderline significance, whereas others such as age tended to predict outcome in a subgroup analysis of the study population. Third, a significant proportion of the patients did not have the hematocrit level at the time of CMR study and thus, the ECV could not be calculated with the pre- and post-contrast results. A group of investigators have advocated the calculation of "synthetic ECV" using blood pool T1 relaxation time instead of the real hematocrit level (38), but this again needs a real hematocrit value to validate the derivation equation of a "calculated" hematocrit value. Last, the native T1 value should be interpreted with caution, because normal values for native T1 may vary according to each center and measurements that are highly influenced by CMR environment, including the scanner and the protocol. The cutoff native T1 values might not be applicable to other imaging centers, and this was one of the reasons that we compared the native T1 values between AS patients and the control subjects.

CONCLUSIONS

High native T1 value on noncontrast T1 mapping CMR is an independent predictor of worse clinical outcome in patients with significant AS. Assessment of the degree of DMF using native T1 value on CMR in AS patients may provide further risk stratification over known predictors of outcome.

FIGURE 6 **Receiver-Operating Characteristic Curve Analysis With 4 Sequential Models Including AV Area, EuroSCORE II, LGE, and Native T1 Value**



Model	*c*-index	*p* for comparison*
1: Indexed AVA	0.56 (0.45 – 0.64)	–
2: Indexed AVA + EuroSCORE II	0.82 (0.74 – 0.88)	<0.001
3: Indexed AVA + EuroSCORE II + LGE	0.88 (0.80 – 0.93)	0.014
4: Indexed AVA + EuroSCORE II + LGE + Highest native T1	0.93 (0.86 – 0.97)	0.037

* P value was calculated using DeLong method.

The group with the highest native T1 value showed incremental prognostic value over known prognostic factors of AS such as smaller AV area, higher EuroSCORE II, and the presence of LGE. AVA = aortic valve area; other abbreviations as in Figures 3 and 5.

ADDRESS FOR CORRESPONDENCE: Dr. Seung-Pyo Lee, Cardiovascular Center, Seoul National University Hospital, 101 Daehak-ro, Jongro-gu, Seoul 110-744, Republic of Korea. E-mail: splee0624@gmail.com.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Myocardial fibrosis ensues following pressure overload in AS, and its degree is a predictor of clinical events. However, methods that enable the noninvasive evaluation of DMF and predict the outcome of the disease are lacking.

TRANSLATIONAL OUTLOOK: Additional research is needed to evaluate whether the appropriate timing of aortic valve replacement can be made on the basis of evaluation or quantification of the degree of myocardial fibrosis using noninvasive imaging. Further noninvasive, and yet simple, imaging studies that could aid the evaluation of DMF should be widened to various cardiac pathologies and to multicenter, international studies.

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KEY WORDS aortic stenosis, cardiac magnetic resonance, native T1 mapping, prognosis

APPENDIX For an expanded Methods section, please see the online version of this paper.