



Accumulation of coronary risk factors is associated with progression of mitral annular calcification in patients undergoing dialysis therapy: A long-term follow-up study

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ABSTRACT

Background: In patients undergoing dialysis therapy, mitral annular calcification (MAC) is a powerful predictor of cardiovascular events and all-cause mortality. However, there is little data on predictors for MAC progression in patients undergoing dialysis therapy.

Methods and results: We retrospectively analyzed 98 hemodialysis-dependent patients in Japanese Red Cross Kumamoto Hospital who underwent routine transthoracic echocardiography (TTE) in 2017. Three patients with history of surgical valve replacement or severe valvular heart diseases were excluded. In the 95 enrolled patients, MAC was detected by TTE in 28 patients (29%). A multivariate logistic regression analysis revealed that duration of hemodialysis therapy was independently associated with presence of MAC (odds ratio [OR]: 1.09; 95% confidence interval [CI]: 1.02–1.16; $p < 0.01$). Among the 95 patients, 72 patients also underwent routine TTE 5 years previously in 2012. In these patients, progression of MAC from 2012 to 2017 was observed in 11 patients (15%). A multivariate logistic regression analysis revealed that number of coronary risk factors (OR: 2.67; 95% CI: 1.24–5.76; $p = 0.01$), baseline MAC diameter (OR: 1.23; 95% CI: 1.05–1.45; $p = 0.01$), and left atrial diameter (OR: 0.81; 95% CI: 0.68–0.95; $p = 0.01$) were significantly associated with progression of MAC. **Conclusions:** Accumulation of coronary risk factors was associated with progression of MAC in patients undergoing dialysis. Management of coronary risk factors may be important for inhibition of MAC progression.

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1. Introduction

Mitral annular calcification (MAC) is a progressive disease that involves fibrosis and calcification of the mitral valve. It is a common finding in 5–10% of the general population [1,2] and up to 35% of patients with coronary artery disease [3]. Valvular dysfunctions can occur in this condition, including mitral regurgitation [4], elevated transmitral gradients [5], and even mitral stenosis [6]. MAC was also shown to be a powerful predictor of cardiovascular events and all-

cause mortality [1,2]. The etiology of MAC is not entirely understood and is likely to be multifactorial. Because MAC is a degenerative process, increased age is an independent predictor of the condition [3,7]. There is ample evidence to support the theory that MAC and atherosclerosis are parts of the same disease process, because of their association with one another, similar associations with other conditions, similar risk factors, and similar effects on cardiovascular risks in terms of aortic, carotid, coronary, and peripheral arterial diseases [3,8,9]. There is also evidence that increased stress on the mitral valve annulus increases the presence, progression, and severity of MAC, leading to observed associations between MAC and systemic hypertension, aortic stenosis, left ventricular hypertrophy, and mitral regurgitation [10–13]. Calcification of cardiac structures is related to metabolic abnormalities, particularly the handling

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of calcium and phosphorus. Therefore, chronic kidney disease (CKD) and end-stage renal disease are important contributing factors associated with MAC [14–17]. However, few studies have investigated the factors for MAC progression, especially in patients undergoing dialysis therapy. The aim of the present study was to clarify the clinical characteristics associated with MAC progression in patients undergoing long-term dialysis therapy as well as factors that can prevent MAC progression.

2. Methods

2.1. Study setting and population

We retrospectively analyzed 98 hemodialysis-dependent patients in Japanese Red Cross Kumamoto Hospital who underwent routine transthoracic echocardiography (TTE) in 2017. Three patients were excluded for history of surgical mitral valve replacement in one patient and severe valvular heart diseases (severe aortic stenosis) in two patients. Thus, 95 patients were enrolled in the study. The 95 patients were divided into two groups by the presence or absence of MAC, and compared. Within the 95 patients, we further selected 72 patients who also underwent routine TTE 5 years previously in 2012. These 72 patients were divided into two groups by the presence or absence of MAC progression, and compared.

2.2. Echocardiographic measurement

All 95 enrolled patients underwent TTE in 2017. For this, two-dimensional and Doppler color flow examinations were performed with a Vivid 7 or Vivid E9 (GE Vingmed, Horten, Norway). The 72 patients who underwent TTE in 2012 were processed with the same echocardiographic systems. By TTE, we evaluated the presence or absence of MAC and several echocardiographic markers. MAC can be seen in the several views of TTE. For instance, Sharma R. et al. diagnosed MAC by parasternal long axis, parasternal short axis views and apical four-chamber view in TTE [17]. To evaluate only the presence of MAC, hence, we were supposed to use multiple views by TTE. However, the

most important purpose of present study was to evaluate the progression of MAC, but not the presence of MAC. And the definition of MAC progression by multiple views of TTE might be complex and not established. By contrast, apical four-chamber view is simple method, and was frequently used for MAC presence [18]. Thus, we used only four-chamber view to examine not only MAC progression but also MAC presence. Therefore, the definition for MAC in our present study was an intense echo-producing structure of ≥ 5 mm located at the junction of the atrioventricular groove and posterior mitral valve leaflet on an apical four-chamber view (Fig. 1) [18,19]. To assess the presence or absence of MAC, two observers, an ultrasonographer and a cardiologist, interpreted the echocardiographic findings. Other than MAC, the left atrial dimension (LAD), left ventricular ejection fraction (LVEF), early diastolic transmitral flow velocity to atrial contraction transmitral flow velocity ratio (E/A ratio), and early diastolic transmitral flow velocity to diastolic early mitral annular velocity ratio (E/e' ratio) were evaluated by TTE. LVEF was measured using the Modified Simpson Method [20]. The definition of valvular diseases including aortic stenosis, aortic regurgitation, mitral stenosis and mitral regurgitation was according to 2014 AHA/ACC guideline [21]. Although there is no accurate definition for MAC progression by TTE, Akiya et al. [22] previously defined MAC progression as a 5 mm increase in MAC diameter. Thus, we defined MAC progression as new onset of MAC or increase in MAC transverse diameter of >5 mm during the 5 years from 2012 to 2017. In addition, we defined “new onset MAC” as de novo expression of MAC larger than 5 mm in transverse diameter in five years' time from 2012 to 2017.

2.3. Data collection

Blood samples and echocardiographic findings were obtained just before performance of hemodialysis therapy. The measured serum biochemical parameters included calcium and phosphorus levels, and the blood samples were stored at -80 °C prior to analysis. Duration of hemodialysis therapy and causes of dialysis were ascertained by reviewing the medical records. Echocardiographic findings and current

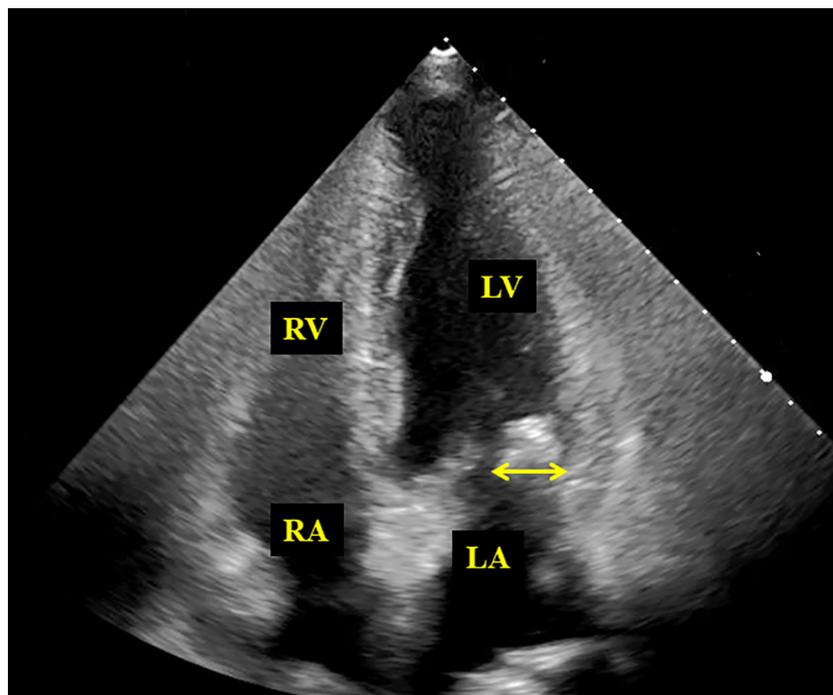


Fig. 1. This was a representative picture of transthoracic echocardiography. Mitral annular calcification (MAC) diameter, located at the junction of the atrioventricular groove and posterior mitral valve leaflet on an apical four-chamber view. The yellow arrow indicates the MAC diameter in the patient. Abbreviation, LA: left atrium, LV: left ventricle, RA: right atrium, RV: right ventricle.

and past medications were also ascertained by reviewing the medical records.

2.4. Definitions of clinical characteristics

The clinical characteristics were defined as follows: body mass index (BMI), body weight/(body height)² (kg/m²); hypertension (HT), patient self-report of a history of systolic blood pressure ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg and/or prior usage of antihypertensive agents; diabetes mellitus (DM), patient self-report of a history of hemoglobin A1c $\geq 6.5\%$ and fasting plasma glucose ≥ 126 mg/dl or casual plasma glucose ≥ 140 mg/dl and/or usage of insulin or diabetes drugs; dyslipidemia, patient self-report of a history of antidyplipidemic drugs, low-density lipoprotein cholesterol ≥ 140 mg/dl, triglycerides ≥ 150 mg/dl and/or high-density lipoprotein cholesterol < 40 mg/dl; smoking, current and past smoking. Several studies have shown that HT, dyslipidemia, smoking, and DM are important risk factors for cardiovascular diseases in Japanese people [23–27]. Thus, HT, dyslipidemia, smoking, and DM were included as coronary risk factors in the present study.

2.5. Statistical analysis

The clinical characteristics of the patients in each group were compared by Student's *t*-test or the chi-square test. The independent variables associated with presence of MAC were assessed by logistic regression analysis. Duration of hemodialysis therapy and classical risk factors for MAC occurrence (high age, sex, number of coronary risk factors) were incorporated into univariate and multivariate logistic regression analysis models. When the independent variables associated with progression of MAC were evaluated, the following variables were initially incorporated into univariate logistic regression analysis models: age, male sex, BMI, baseline MAC diameter, causes of dialysis (diabetic nephropathy, glomerular nephritis, polycystic kidney disease), number of coronary risk factors, duration of hemodialysis therapy, LAD, LVEF, E/e' ratio, usage of calcium channel blocker, angiotensin-converting enzyme inhibitor/angiotensin II receptor antagonist, β -blocker, or calcium carbonate, serum calcium level, and serum phosphorus level. Variables with values of $p < 0.05$ were incorporated into a multivariate logistic regression analysis model.

All analyses were conducted with SPSS for windows, version 24.0. Statistical significance was defined as values of $p < 0.05$. The study protocol conformed to the principles of the Declaration of Helsinki, and was approved by the Institutional Review Board of Japanese Red Cross Kumamoto Hospital (reference number 276/2017). This study is a retrospective observational study, carried out by the opt-out method of website in Japanese Red Cross Kumamoto Hospital.

3. Results

3.1. Clinical characteristics in hemodialysis patients with and without MAC

The clinical characteristics of the patients with and without MAC are shown in Table 1-a. MAC was detected in 28 patients (29%), and its transverse diameter was 12.4 ± 7.4 mm. Duration of hemodialysis therapy was significantly longer in patients with MAC than those without MAC (13.4 ± 8.6 years vs. 7.7 ± 8.4 years; $p < 0.01$). There were no significant differences in other baseline characteristic factors, causes of dialysis, and laboratory findings between the two groups. In the echocardiographic findings, E/e' ratio (21.8 ± 10.2 vs. 16.3 ± 6.3 ; $p < 0.01$), the rate of moderate aortic regurgitation (AR) (7% vs. 0%, $p = 0.03$) and mitral stenosis (MS) (7% vs. 0%, $p = 0.03$) was significantly higher in patients with MAC than in those without MAC (Table 1-a). There were no significant differences in the rate of moderate aortic stenosis (AS) (21% vs. 12%, $p = 0.23$) and mitral regurgitation (MR) (7% vs. 7%, $p = 0.96$). In terms of drug usage, only use of calcium channel

Table 1-a
Clinical characteristics of patients according to the presence or absence of MAC.

Variables	MAC		p-Value
	Presence (n = 28)	Absence (n = 67)	
Baseline characteristics			
Age, years	65.0 \pm 10.7	62.6 \pm 13.2	0.38
Male gender (%)	15 (54)	36 (54)	0.56
BMI, kg/m ²	20.9 \pm 3.3	21.2 \pm 2.9	0.64
Atrial fibrillation, n (%)	0 (0)	2 (3)	0.24
HT, n (%)	20 (71)	55 (82)	0.44
DM, n (%)	7 (25)	16 (24)	0.85
Dyslipidemia, n (%)	5 (18)	11 (16)	0.89
Smoking, n (%)	10 (36)	15 (22)	0.34
History of PCI, n (%)	1 (4)	4 (6)	0.63
History of CABG, n (%)	2 (7)	2 (3)	0.36
History of myocardial infarction, n (%)	3 (11)	6 (9)	0.79
History of stroke, n (%)	2 (7)	3 (4)	0.60
Number of coronary risk factors, (n)	1.50 \pm 1.20	1.45 \pm 1.06	0.83
Duration of hemodialysis therapy, years	13.4 \pm 8.6	7.7 \pm 8.4	<0.01
Causes of dialysis			
Diabetic nephropathy, n (%)	6 (21)	10 (15)	0.44
Glomerular nephritis, n (%)	12 (43)	27 (40)	0.82
Polycystic kidney disease, n (%)	2 (7)	5 (7)	0.96
Nephrosclerosis, n (%)	0 (0)	5 (7)	0.14
Echocardiographic findings			
Left atrial dimension, mm	41.8 \pm 5.9	40.6 \pm 6.2	0.39
Left ventricular ejection fraction (%)	60.1 \pm 11.5	62.3 \pm 8.3	0.28
E/A ratio	0.9 \pm 0.3	1.0 \pm 0.5	0.45
E/e' ratio	21.8 \pm 10.2	16.3 \pm 6.3	<0.01
Moderate AS, n (%)	6 (21)	8 (12)	0.23
Moderate AR, n (%)	2 (7)	0 (0)	0.03
Moderate MS, n (%)	2 (7)	0 (0)	0.03
Moderate MR, n (%)	2 (7)	5 (7)	0.96
Current medications			
CCB, n (%)	13 (46)	49 (73)	0.01
ACE-I/ARB, n (%)	11 (39)	33 (49)	0.37
β -Blocker, n (%)	4 (14)	14 (21)	0.45
Calcium carbonate, n (%)	16 (57)	30 (45)	0.27
Current laboratory findings			
Serum calcium levels (mg/dl)	8.9 \pm 1.2	8.6 \pm 0.9	0.24
Serum phosphorus levels (mg/dl)	5.4 \pm 1.1	5.4 \pm 1.3	0.92

Abbreviations: MAC, mitral annular calcification; BMI, body mass index; HT, hypertension; DM, diabetes mellitus; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; AS, aortic stenosis; AR, aortic regurgitation; MS, mitral stenosis; MR, mitral regurgitation; CCB, calcium channel blocker; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

p-Values were obtained by Student's *t*-test or the chi-square test.

blockers was significantly lower in patients with MAC than in those without MAC (46% vs. 73%; $p = 0.01$; Table 1-a). A multivariate logistic regression analysis revealed that duration of hemodialysis therapy was significantly associated with presence of MAC (odds ratio [OR]: 1.09; 95% confidence interval [CI]: 1.02–1.16; $p < 0.01$; Table 1-b).

3.2. Clinical characteristics in hemodialysis patients with and without MAC progression

Among the 95 enrolled patients, 72 patients also underwent routine TTE 5 years previously in 2012. Of these 72 patients, 17 patients (24%) already had MAC in 2012, and its transverse diameter was 10.2 ± 4.0 mm at that time. The transverse diameter of MAC tended to increase during the 5 years from 2012 to 2017, but the change was not significant (10.2 ± 4.0 mm vs. 12.4 ± 7.4 mm; $p = 0.05$).

We further divided these 72 patients into two groups: those with MAC progression ($n = 11$) and those without MAC progression ($n = 61$). The clinical characteristics of the patients with and without MAC progression are compared in Table 2-a. The numbers of coronary risk factors were significantly higher in the progression group than in the non-progression group (1.91 ± 0.83 vs. 1.18 ± 0.99 ; $p = 0.03$). The baseline MAC diameter in 2012 was significantly larger in the progression group than in the non-progression group (6.6 ± 6.9 mm vs.

Table 1-b

Factors associated with presence of MAC.

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-Value	OR (95% CI)	p-Value
Age (≥ 65 y) (+)	1.76 (0.70–4.35)	0.23	1.59 (0.23–1.75)	0.37
Male gender (+)	0.99 (0.41–2.38)	0.99	0.76 (0.25–2.31)	0.63
Number of coronary risk factors (/1)	1.09 (0.73–1.61)	0.68	1.29 (0.79–2.11)	0.32
Duration of hemodialysis therapy, years (/1 year)	1.07 (1.01–1.12)	0.02	1.09 (1.02–1.16)	<0.01

p-Values were obtained by logistic regression analysis.

2.2 \pm 3.9 mm; $p < 0.01$). The rate of coronary artery bypass graft was significantly higher in the progression group than in the non-progression group (18% vs. 2%, $p = 0.01$). For the echocardiographic findings, LAD was significantly lower in the progression group than in the non-progression group (34.6 \pm 4.3 mm vs. 38.4 \pm 5.4 mm; $p = 0.03$). There were no significant differences for duration of hemodialysis therapy, causes of dialysis, drug usage, and laboratory findings between

the two groups. A multivariate logistic regression analysis revealed that number of coronary risk factors (OR: 2.67; 95% CI: 1.24–5.76; $p = 0.01$), baseline MAC diameter (OR: 1.23; 95% CI: 1.05–1.45; $p = 0.01$), and LAD (OR: 0.81; 95% CI: 0.68–0.95, $p = 0.01$) were significantly and independently associated with MAC progression (Table 2-b).

Table 2-a

Comparisons of clinical characteristics between the MAC progression group and non-progression group.

Variables	Progression group (n = 11)	Non-progression group (n = 61)	p-Value
Baseline characteristics			
Age, years	67.4 \pm 10.5	64.3 \pm 11.3	0.40
Male gender (%)	7 (64)	27 (44)	0.07
BMI, kg/m ²	21.0 \pm 2.2	20.9 \pm 3.1	0.92
Atrial fibrillation, n (%)	1 (9)	1 (2)	0.17
The diameter of MAC (mm)	6.6 \pm 6.9	2.2 \pm 3.9	<0.01
HT, n (%)	10 (91)	43 (70)	0.02
DM, n (%)	3 (27)	10 (16)	0.05
Dyslipidemia, n (%)	3 (27)	6 (10)	0.06
Smoking, n (%)	5 (45)	12 (20)	0.13
History of PCI, n (%)	0 (0)	4 (7)	0.38
History of CABG, n (%)	2 (18)	1 (2)	0.01
History of myocardial infarction, n (%)	2 (18)	5 (8)	0.30
History of stroke, n (%)	1 (9)	3 (5)	0.58
Number of coronary risk factors	1.91 \pm 0.83	1.18 \pm 0.99	0.03
Duration of hemodialysis therapy, years	15.0 \pm 7.3	13.6 \pm 8.5	0.57
Causes of dialysis			
Diabetic nephropathy, n (%)	2 (18)	5 (8)	0.30
Glomerular nephritis, n (%)	4 (36)	31 (51)	0.38
Polycystic kidney disease, n (%)	2 (18)	4 (7)	0.20
Nephrosclerosis, n (%)	0 (0)	3 (5)	0.45
Past echocardiographic findings			
Left atrial dimension, mm	34.6 \pm 4.3	38.4 \pm 5.4	0.03
Left ventricular ejection fraction (%)	65.0 \pm 4.7	64.9 \pm 7.0	0.96
E/A ratio	0.80 \pm 0.25	0.93 \pm 0.27	0.15
E/e' ratio	16.0 \pm 7.3	14.6 \pm 4.5	0.39
Moderate AS, n (%)	0 (0)	4 (7)	0.38
Moderate AR, n (%)	0 (0)	1 (2)	0.67
Moderate MS, n (%)	0 (0)	1 (2)	0.67
Moderate MR, n (%)	0 (0)	1 (2)	0.67
Past medications			
CCB, n (%)	7 (64)	39 (64)	0.98
ACE-I/ARB, n (%)	8 (73)	33 (54)	0.25
β -Blocker, n (%)	3 (27)	8 (13)	0.23
Calcium carbonate, n (%)	6 (55)	32 (52)	0.90
Past laboratory findings			
Serum calcium levels (mg/dl)	9.0 \pm 0.9	8.9 \pm 0.8	0.86
Serum phosphorus levels (mg/dl)	5.3 \pm 1.2	5.4 \pm 1.2	0.78

Abbreviations: MAC, mitral annular calcification; BMI, body mass index; HT, hypertension; DM, diabetes mellitus; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; AS, aortic stenosis; AR, aortic regurgitation; MS, mitral stenosis; MR, mitral regurgitation; CCB, calcium channel blocker; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

The data on past echocardiographic findings, past medications, and past laboratory findings were obtained in 2012.

p-Values were obtained by Student's *t*-test or the chi-square test.

4. Discussion

The novel findings in the present study were: (1) duration of hemodialysis therapy was significantly associated with presence of MAC; and (2) accumulation of coronary risk factors and baseline MAC diameter were significantly associated with progression of MAC.

Aging is well known as a conventional risk factor for presence of MAC regardless of the presence of CKD [3,7,28]. Several studies also showed that aging is associated with presence of MAC in dialysis-dependent patients [29,30]. However, the present study found that aging was not associated with presence of MAC in dialysis-dependent patients. Furthermore, we found that female sex and coronary risk factors, as other well-established classical risk factors for MAC, had no association with presence of MAC. Our study population only contained dialysis-dependent patients and their durations of dialysis therapy were very long (13 years in patients with MAC and 8 years in patients without MAC). In contrast, the periods of hemodialysis in the previous studies were all <5 years, indicating markedly shorter durations of dialysis therapy in the previous studies compared with the present study. Because long-term hemodialysis was reported to be an important risk factor for MAC incidence [29,31], we speculate that the effect of hemodialysis on MAC incidence was larger in the present study compared with the previous studies. Thus, the strong effect of long-term hemodialysis on MAC incidence may have obscured the effects of classical risk factors in the present study.

Interestingly, the present study clearly demonstrated that accumulation of coronary risk factors was independently associated with progression of MAC, but not with presence of MAC, indicating that the incidence and progression of MAC have different pathophysiologies. Previous *in vivo* and *in vitro* studies attributed valve calcification to valve myofibroblast activation and transdifferentiation into an osteoblast-like cell type [32–34], leading to changes in cell phenotype triggered by an atherosclerosis-like process [33]. Once activated, valve myofibroblasts secrete several inflammatory cytokines that can promote valve calcification [35]. Thus, the self-perpetuating process of calcification was considered to be less dependent on cardiovascular risk factors than on activated valve myofibroblasts. In addition, there are various reports on associations between coronary risk factors and presence of MAC [3,8,9]. Elmariah et al. [36] reported that coronary risk factors in non-dialysis-dependent patients can even induce progression of MAC. By contrast, the present study demonstrated that long-term hemodialysis had a strong effect on incidence of MAC, but not progression of MAC. Because long-term dialysis had no effect on progression of MAC in the present study, the effect of coronary risk factors on progression of MAC may have become obvious. On the other hand, Massera et al. [37] reported no association between coronary risk factors and progression of MAC. The observational term of this previous report was only 2 years. In contrast, that of our present

Table 2-b

Factors associated with progression of MAC.

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-Value	OR (95% CI)	p-Value
Age (≥65 y) (+)	2.13 (0.51–9.09)	0.30	Not selected	
Male gender (+)	2.22 (0.58–8.33)	0.24	Not selected	
BMI (/1 kg/m ²)	1.01 (0.81–1.26)	0.92	Not selected	
Baseline MAC diameter (/1 mm)	1.17 (1.03–1.33)	0.01	1.23 (1.05–1.45)	0.01
Diabetic nephropathy, n (%)	2.50 (0.42–14.29)	0.32	Not selected	
Glomerular nephritis, n (%)	0.55 (0.15–2.08)	0.38	Not selected	
Polycystic kidney disease, n (%)	3.13 (0.51–20.00)	0.22	Not selected	
Number of coronary risk factors (/1)	1.95 (1.05–3.63)	0.03	2.67 (1.24–5.76)	0.01
Duration of hemodialysis therapy, years (/1 year)	1.02 (0.94–1.10)	0.60	Not selected	
LAD (/1 mm)	0.87 (0.77–0.99)	0.04	0.81 (0.68–0.95)	0.01
LVEF (/1%)	1.01 (0.94–1.10)	0.77	Not selected	
E/e' ratio (/1)	1.03 (0.95–1.11)	0.47	Not selected	
CCB, (+)	0.99 (0.26–3.70)	0.99	Not selected	
ACE-I/ARB, (+)	2.27 (0.54–9.09)	0.26	Not selected	
β-Blocker, (+)	2.50 (0.54–11.11)	0.24	Not selected	
Calcium carbonate, (+)	1.09 (0.30–4.00)	0.90	Not selected	
Serum calcium levels (mg/dl)	1.08 (0.46–2.54)	0.86	Not selected	
Serum phosphorus levels (mg/dl)	0.92 (0.52–1.63)	0.78	Not selected	

p-Values were obtained by logistic regression analysis.

study was 5 years. It might take long term to reveal the effect of coronary risk factors on MAC progression.

Elmariah et al. [36] revealed that baseline MAC severity was an important risk factor for MAC progression in non-dialysis-dependent patients. The same phenomenon was found in dialysis-dependent patients in the present study. Severe MAC is known to restrict mitral annular motion, and increase mitral inflow velocity and stress on the mitral valve [38], leading to MAC occurrence [10,11]. This may be the reason why baseline MAC diameter was associated with MAC progression in the present study.

Previous study reported that MAC is significantly associated with left atrial (LA) enlargement [39], and our present study also showed that LA dimension tended to be larger in MAC presence group than in MAC absence group. We speculate that LA pressure overload by MAC presence could induce LA enlargement, but not that LA enlargement induces the formation of MAC. To our knowledge, by contrast, there is no data about the association between LA volume and MAC progression. Our present study demonstrated that lower LA dimension was significantly associated with MAC progression. Because LA dilatation is inversely associated with LA function [40], our study indicated that better LA function, represented by lower LA dimension, could influence only MAC progression, but not MAC presence. The measurement of only LA dimension was not enough to evaluate LA remodeling. Thus, we should evaluate LA volume, ejection fraction or/and longitudinal strain to examine LA function and remodeling. However, we couldn't evaluate these measurements retrospectively because we didn't take optimal echocardiographic images for evaluation of LA function.

Prospective studies found that MAC was independently associated with cardiovascular disease, cardiovascular death, and all-cause death after adjustment for traditional cardiovascular risk factors [1,2]. CKD including hemodialysis is also known to be a high-risk factor for cardiovascular complications [41]. Several studies have shown that management of coronary risk factors can improve prognosis, even in dialysis-dependent patients [42–45]. Our study revealed that accumulation of coronary risk factors was associated with MAC progression, indicating that management of coronary risk factors in dialysis-dependent patients may improve their prognosis by preventing not only cardiovascular events, but also mitral valvular diseases such as MAC.

The present study has several limitations. First, the results should be interpreted with caution because the study was retrospective and observational, making it difficult to clarify cause–effect relationships. Second, we could not obtain data for C reactive protein, a representative biomarker of inflammation, in 2012. Thus, we could not evaluate the precise association between systemic inflammation and progression of

MAC. Third, the study was performed at a single center, and the sample size was relatively small. Thus, there may be bias related to the sample size. In future, a large-scale clinical trial is needed to clarify the risk factors for MAC progression in dialysis-dependent patients.

5. Conclusions

Accumulation of coronary risk factors was significantly associated with progression of MAC in patients undergoing dialysis. A further interventional study is needed to examine whether optimal management of coronary risk factors in dialysis-dependent patients can be useful for inhibition of MAC progression.

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