

ORIGINAL ARTICLE

A 2-Year Prospective Study on the Differences in Prognostic Factors for Major Adverse Cardiovascular, Cerebrovascular and Renal Events Between Patients with Mild and Severe Chronic Kidney Disease

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Abstract

Purpose/Method: No studies have reported on prognostic markers in patients with chronic kidney disease (CKD) according to the severity of the disease. Therefore, in this multicenter, prospective trial performed as part of the Gunma CKD SPECT Multicenter Study, we recruited 311 patients with CKD (eGFR <60 mL/min/1.73 m²) including 50 patients on hemodialysis and followed them for 2 years. The study sample underwent stress ^{99m}Tc-tetrofosmin SPECT for suspected or possible ischemic heart disease. We evaluated the summed stress score (SSS), summed rest score (SRS), summed difference score (SDS) and cardiac function with electrocardiogram-gated SPECT. Then, we compared the differences in prognostic markers for major adverse cardiac, cerebrovascular, and renal events (MACCRE) between patients with mild CKD (30 mL/min/1.73 m² ≤ eGFR <60 mL/min/1.73 m²; n=184) and those with severe CKD (eGFR <30 mL/min/1.73 m²; n=97).

Results: Of 281 patients available for analysis, 91 experienced MACCRE. In a multivariate Cox proportional hazards analysis of factors related to MACCRE, in patients with mild CKD the significant prognostic markers were SDS (*P*=0.002) and end-systolic volume (ESV, *P*=0.034); and in the patients with severe CKD, they were eGFR (*P*=0.03) and diabetes-mellitus (DM, *P*=0.023).

Conclusions: Our findings indicate that SDS and ESV are significant prognostic markers for MACCRE in patients with mild CKD and eGFR and DM are significant prognostic markers in patients with severe CKD.

Keywords: Cardiovascular events, Cerebrovascular and renal events, Chronic kidney disease, Hemodialysis, Ischemic heart disease, Nuclear imaging

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Cardiovascular events include a superimposed thrombus on top of a ruptured plaque (1, 2). The risk of such events is higher in chronic kidney disease (CKD), which increases platelet aggregation, platelet reactivity, and blood thrombogenicity (3). Therefore, researchers have recently recog-

nized that impaired kidney function is an independent risk factor for all-cause mortality and adverse cardiovascular outcomes, including myocardial infarction, stroke, and progression of heart failure (4–8).

Myocardial perfusion single-photon emission computed

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tomography (SPECT) can accurately and noninvasively diagnose ischemic heart disease and other cardiac conditions (9–11). In addition, quantitative ECG-gated SPECT (QGS) with the computer program QGS is useful for measuring left ventricular dimensions and the left ventricular ejection fraction (LVEF) (12–14). Studies have evaluated the prognostic value of combined stress myocardial perfusion SPECT and QGS for predicting major cardiac events (9, 10, 15). A number of studies have also used combined imaging to assess the prognosis of patients with CKD (16–24). Based on the results of these studies, scintigraphic parameters were shown to be independent predictors of cardiac events, including cardiac death, heart failure, and acute myocardial infarction. However, little is known about the prognostic value of these imaging methods for patients in different stages of CKD, including patients with advanced renal dysfunction, such as those on hemodialysis. Accordingly, we performed a 2-year, prospective, multicenter cohort trial in CKD patients, including patients on hemodialysis, to evaluate whether stress myocardial perfusion SPECT and QGS quantification of SPECT could predict major adverse cardiovascular, cerebrovascular, and renal events (MACCRE). In the present study, we compared differences in prognostic markers for MACCRE between patients with mild and severe CKD.

Materials and methods

Patients and study protocol

This was a prospective multicenter cohort trial performed according to the Gunma CKD SPECT Study protocol. The enrollment period was from August 2010 to July 2012. Stress/rest myocardial perfusion SPECT was performed in 311 patients including 50 patients on hemodialysis within 2 months of enrollment. Imaging data, background factors, treatment before SPECT, and the results of other examinations were recorded. The study was completed in 2014, and this report provides the results from 2 years of follow-up. To access the relation between MACCRE and the severity of CKD, we divided patients into 2 groups on the basis of the estimated glomerular filtration rate (eGFR): those with mild CKD ($30 \text{ min/mL/1.73 m}^2 \leq \text{eGFR} < 60 \text{ min/mL/1.73 m}^2$) and those with severe CKD ($\text{eGFR} < 30 \text{ min/mL/1.73 m}^2$).

The inclusion criteria were as follows: 1) age 20 years or older; 2) patients scheduled to undergo myocardial perfusion SPECT and QGS because of suspected ischemic heart disease; 3) eGFR less than $60 \text{ min/mL/1.73 m}^2$; and 4) at least 1 risk factor for coronary artery disease (hypertension, diabetes mellitus [DM], dyslipidemia, peripheral artery disease, smoking ≥ 10 cigarettes/d, family history of coronary artery disease, and history of ischemic stroke). The exclusion criteria were as follows: 1) age older than 80 years; 2) severe valvular heart disease; 3) hypertrophic cardiomyopathy or dilated

cardiomyopathy; 4) allergy to tetrofosmin or its analogs; 5) severe arrhythmia that could interfere with QGS; 6) bronchospastic pulmonary disease or contraindications for vasodilator infusion; and 7) patients judged by the attending physician to be unsuitable for the study for any other reason.

Ethics

Approval from the review boards of all facilities involved in this study is compulsory. In accordance with the Declaration of Helsinki 2008, all patients will provide written, informed consent to participate in all study protocols before enrolment.

Myocardial perfusion SPECT and evaluation

The patients underwent stress and resting SPECT with $^{99\text{m}}$ Tc-tetrofosmin. Exercise or pharmacological stress tests or both were performed with either a stress-rest or a rest-stress sequence. Each participating hospital used a standard myocardial SPECT protocol. However, the number of detectors, matrix size, number of steps, and camera rotation range were not specified, and the acquisition conditions followed the protocol of each institution. Electrocardiogram-gated SPECT was performed under resting conditions in all patients and also under stress conditions in some patients. Stress (exercise or pharmacological) and rest blood pressure and heart rate were recorded. Gated SPECT findings were quantified with QGS software (Cedars Sinai Medical Center, Los Angeles, CA) at all participating institutions (12–14). The images and image processing procedures were surveyed separately.

The myocardial perfusion image of each participant was divided into 17 segments on each SPECT image, as recommended by the American Heart Association (25). Regional tracer uptake was assessed semiquantitatively by using the following 5-point scale: 0=normal uptake; 1=mildly reduced uptake; 2=moderately reduced uptake; 3=severely reduced uptake; and 4=no uptake. The sum of the scores of the 17 segments in the stress and resting images was calculated as the summed stress score (SSS) and summed rest score (SRS), respectively. Then, the summed difference score (SDS) was calculated as the difference between the SSS and SRS. All myocardial SPECTs were assessed by the core laboratory.

The left ventricular end-diastolic volume (EDV) and end-systolic volume (ESV) and left ventricular ejection fraction (LVEF) were obtained from QGS analysis. Heart rate and blood pressure were also monitored during the stress tests.

Follow-up

Patients were followed up for 2 years after stress myocardial perfusion SPECT and QGS. The endpoint of the study was the incidence of MACCRE, which was defined as the occurrence of cardiac death, sudden death, non-fatal myocardial infarction

(MI), hospitalization for heart failure, cerebrovascular accidents, revascularization, renal events (ie, initiation of hemodialysis or kidney transplantation), and other cardiovascular disease.

Revascularization immediately after myocardial SPECT is included as a cardiac event.

Other cardiovascular diseases indicate unstable angina pectoris, percutaneous transluminal angioplasty and aortic event. Hospitalization for heart failure was defined as that the appearance of cardiac pump failure caused the heart failure findings including dyspnea, fatigue, edema, decreased exercise tolerance and congestion on chest X-ray, then hospitalization was needed. It was the same in patients with hemodialysis.

Statistical analysis

Analyses were performed with JMP software (SAS Institute Inc., Cary, NC). Results are expressed as the mean \pm SD. In all analyses, $P < 0.05$ was considered statistically significant. Categorical data were compared between 2 groups by using Fisher's exact test or the chi-square test, and differences

between continuous variables were evaluated by using the unpaired t test. The groups of patients with mild or severe CKD were each divided into a MACCRE group and a non-MACCRE group. Univariate Cox proportional hazards models were created to identify independent predictors of MACCRE by using variables such as clinical characteristics, risk factors, laboratory data, and the stress myocardial perfusion SPECT and QGS parameters. Subsequently, multivariate Cox proportional hazards analysis was performed in the groups of patients with mild or severe CKD.

As cut-off values of various parameters for predicting MACCRE, we used SDS=4, ESV=105 mL, and eGFR=15 mL/min/1.73m².

Results

Clinical profile and adverse events

We were able to follow 281 of the 311 patients for 2 years and obtain reliable information about their outcome from the patients themselves, their families, and/or the participating hospitals (Figure 1). The group of patients with mild CKD ($n=184$) consisted of 144 men and 40 women with a mean age of 72 years (range, 55–82 years); and the group of patients with severe CKD ($n=97$) consisted of 64 men and 33 women with a mean age of 66 years (range, 49–76 years). Of the 281 patients, 91 experienced MACCRE (Table 1).

Results in the group of patients with mild CKD

Comparison of clinical characteristics and stress myocardial perfusion SPECT and QGS parameters between the MACCRE and non-MACCRE groups

The clinical characteristics and scintigraphic parameters of the patients with mild CKD in the MACCRE and non-MACCRE groups are shown in Table 2. Age, sex, height, body weight, body mass index, hemodialysis rate, history of

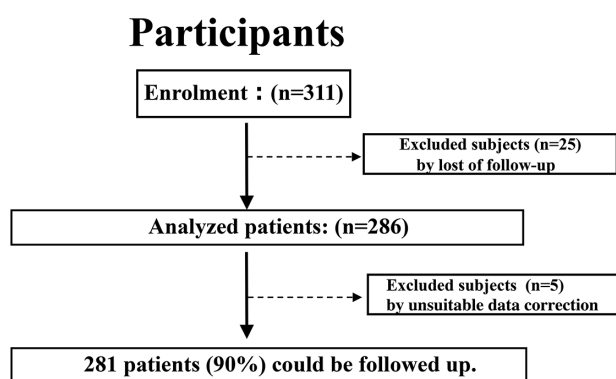


Figure 1 Patients flow.

Table 1 MACCRE between mild and severe CKD patients

	eGFR \geq 30 min/mL/1.73 m ² (n=184)	eGFR<30 min/mL/1.73 m ² (n=97)	<i>P</i>
1) Cardiac death: (n=13)	6	7	0.145
2) Sudden death: (n=3)	2	1	1
3) Non-fatal myocardial infarction: (n=3)	3	0	0.554
4) Hospitalization for heart failure: (n=11)	2	9	0.002
5) Cerebrovascular accident: (n=7)	3	4	0.239
6) Need for revascularization: (n=36)	29	7	0.042
7) Renal events: (n=12)	3	9	0.004
8) Other cardiovascular events: (n=6)	4	2	1
Total	52	39	

CKD: chronic kidney disease

Other cardiovascular events: 3 patients with unstable angina pectoris, 2 patients with percutaneous transluminal angioplasty and 1 patient with a ruptured abdominal aortic aneurysm.

Table 2 Clinical characteristics and scintigraphic parameters of the MACCRE and non-MACCRE groups in mild CKD patients (eGFR \geq 30 mL/min/1.73 m²)

	non-MACCRE group (n=132)	MACCRE group (n=52)	P Value
Age, years	71 \pm 6	72 \pm 7	0.744
Male gender, n (%)	100 (76)	44 (85)	0.162
Height, cm	159 \pm 17	161 \pm 7	0.240
Weight, kg	61 \pm 13	61 \pm 10	0.974
BMI, kg/m ²	24 \pm 3	24 \pm 4	0.410
Hemodialysis	0 (0)	0 (0)	
Hypertension	100 (76)	37 (71)	0.519
Diabetes mellitus	37 (29)	23 (44)	0.035
Dyslipidemia	71 (55)	26 (50)	0.215
Prior MI	18 (14)	7 (13)	0.975
Hb, g/dl	14.1 \pm 9.3	13.1 \pm 1.8	0.242
HbA1c, %	6.0 \pm 1.5	6.1 \pm 1.6	0.848
eGFR, mL/min/1.73m ²	49 \pm 8	48 \pm 11	0.562
TG, mg/dl	153 \pm 75	155 \pm 101	0.920
LDL, mg/dl	101 \pm 30	106 \pm 33	0.399
HDL, mg/dl	49 \pm 20	46 \pm 10	0.331
SPECT data			
Exercise stress	44 (34)	18 (35)	0.976
Pharmacological stress	84 (66)	33 (63)	0.982
EDV, mL	92 \pm 46	117 \pm 75	0.032
ESV, mL	42 \pm 35	67 \pm 69	0.013
LVEF, %	60 \pm 14	51 \pm 19	0.007
SSS	3.3 \pm 6.9	5.1 \pm 7.4	0.129
SRS	2.7 \pm 6.2	3.3 \pm 6.1	0.588
SDS	0.54 \pm 2.1	1.8 \pm 4.1	0.041
Medical treatment			
ACE-I and/or ARB	31 (24)	15 (29)	0.851
β -blocker	10 (8)	15 (29)	0.001
Vasodilators	16 (13)	10 (19)	0.213
Statin	30 (23)	29 (42)	<0.0001
Antidiabetic drugs	32 (25)	22 (42)	0.103

Values are mean \pm SD or number (%).

CKD: chronic kidney disease, BMI: body mass index, MI: myocardial infarction, eGFR: estimated glomerular filtration rate, TG: triglyceride, LDL: low-density lipoprotein, HDL: high-density lipoprotein, SPECT: single photon emission computed tomography, SSS: summed stress score, SRS: summed rest score, SDS: summed difference score, EDV: end-diastolic volume, SDV: end-systolic volume, LVEF: left ventricular ejection fraction, ACE-I: angiotensin-converting enzyme inhibitor, ARB: angiotensin receptor blocker.

hypertension, dyslipidemia, prior MI, and laboratory parameters were similar in the 2 groups, but diabetes mellitus (DM) was significantly more common in the MACCRE group than in the non-MACCRE group.

Data from the perfusion SPECT studies showed that EDV, ESV, and SDS were significantly higher in the MACCRE group than in the non-MACCRE group, whereas LVEF was significantly lower. The groups showed no significant differences in the frequency of exercise stress or pharmaco-

logical stress.

Medications such as beta-blockers and statins were used more frequently in the MACCRE group than in the non-MACCRE group.

Univariate Cox proportional hazards models for MACCRE

The results of univariate Cox proportional hazards analysis of factors related to MACCRE in patients with mild CKD are shown in Table 3. EDV, ESV, LVEF, SDS, and treatment with beta-blockers, statins, or antidiabetic drugs were significant

Table 3 Univariate Cox proportional hazards analysis for MACCRE in mild CKD patients (eGFR \geq 30 mL/min/1.73 m²)

Variate	Hazard ratio	95% CI	P Value
Age, years	1.004	0.962-1.052	0.854
Male gender, n (%)	1.601	0.797-3.672	0.197
BMI, kg/m ²	0.964	0.879-1.052	0.417
Hypertension	0.809	0.453-1.519	0.495
Diabetes mellitus	1.702	0.975-2.936	0.061
Dyslipidemia	0.800	0.463-1.383	0.422
Prior MI	0.961	0.396-1.994	0.921
Hb, g/dl	0.949	0.817-1.015	0.299
HbA1c, %	1.025	0.816-1.173	0.794
eGFR, mL/min/1.73 m ²	0.989	0.960-1.021	0.486
TG, mg/dl	1	0.997-1.004	0.834
LDL, mg/dl	1.004	0.995-1.013	0.353
HDL, mg/dl	0.989	0.954-1.012	0.426
SPECT data			
Exercise stress	1.031	0.570-1.802	0.917
Pharmacological stress	0.902	0.519-1.616	0.723
EDV, mL	1.005	1.001-1.009	0.016
ESV, mL	1.007	1.002-1.010	0.004
LVEF, %	0.975	0.959-0.991	0.003
SSS	1.026	0.990-1.059	0.146
SRS	1.008	0.964-1.047	0.693
SDS	1.118	1.038-1.186	0.005
Medical treatment			
ACE-I and/or ARB	1.246	0.664-2.224	0.479
β -blocker	2.990	1.591-5.254	0.001
Vasodilators	1.520	0.720-2.907	0.255
Statin	2.039	1.163-3.522	0.014
Antidiabetic drugs	1.839	1.048-3.177	0.034

All abbreviations as in Table 2.

Table 4 Significant predictors for MACCRE by Cox multivariate analysis (eGFR \geq 30 mL/min/1.73 m²)

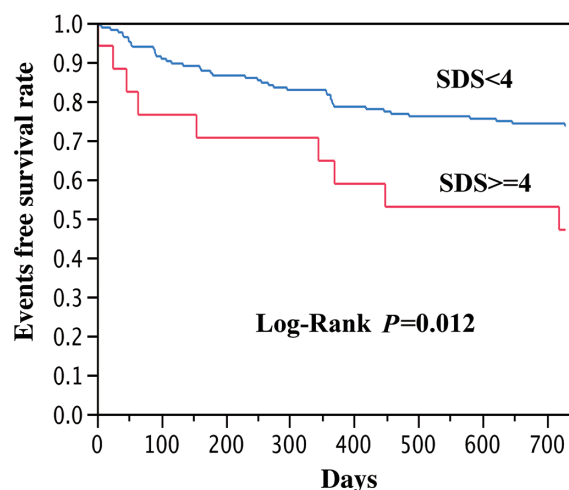
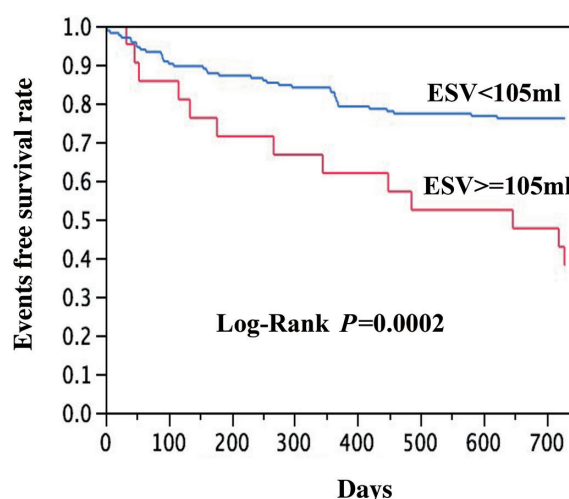
Variate	Hazard ratio	95% CI	P Value
SSS	0.944	0.887-0.998	0.042
SDS	1.163	1.059-1.273	0.002
ESV, mL	1.028	1.002-1.054	0.034
EDV, mL	0.984	0.964-1.003	0.097
LVEF, %	0.996	0.968-1.023	0.783
Diabetes mellitus	1.601	0.897-2.821	0.110

All abbreviations as in Table 2.

factors.

Multivariate Cox analysis for MACCRE

Significant predictors for MACCRE in patients with mild CKD found by Cox multivariate analysis are shown in Table 4. According to multivariate analysis, the most important

**Figure 2** Influence of SDS on the 2-year event-free rate for major adverse cardiac, cerebrovascular, and renal events in patients with chronic kidney disease.**Figure 3** Influence of ESV on the 2-year event-free rate for major adverse cardiac, cerebrovascular, and renal events in patients with chronic kidney disease.

predictors of MACCRE were the SDS ($P=0.002$, hazard ratio [HR]=1.163) and ESV ($P=0.034$, HR=1.028).

MACCRE-free survival rate

Figure 2 and 3 show Kaplan-Meier curves for the MACCRE-free survival rate in patients with mild CKD after 2 years of follow-up. The event-free rate was 0.74 in the group with an SDS under 4 and 0.47 in the group with an SDS greater than or equal to 4 ($P=0.012$, log-rank test; Figure 2). In the group with an ESV less than 105 mL, the event-free rate was 0.98, and in the group with an ESV equal to or greater than 105 mL, it was 0.76 ($P=0.0002$, log-rank test; Figure 3).

Table 5 Clinical characteristics and scintigraphic parameters of the MACCRE and non-MACCRE groups in severe CKD patients (eGFR<30 mL/min/1.73 m²)

	non-MACCRE group (n=58)	MACCRE group (n=39)	P Value
Age, years	66 ± 10	66 ± 9	0.814
Male gender	38 (65)	26 (67)	0.861
BMI, kg/m ²	24 ± 3	25 ± 4	0.340
Hemodialysis	24 (41)	20 (51)	0.337
Hypertension	49 (84)	33 (85)	0.986
Diabetes mellitus	16 (28)	19 (50)	0.034
Dyslipidemia	20 (34)	17 (44)	0.365
Prior MI	5 (9)	5 (13)	0.505
Hb, g/dl	11.4 ± 1.8	10.7 ± 1.7	0.044
HbA1c, %	5.9 ± 1.0	6.2 ± 0.9	0.144
eGFR, mL/min/1.73 m ²	14 ± 9	9 ± 6	0.007
TG, mg/dl	132 ± 125	112 ± 601	0.293
LDL, mg/dl	91 ± 27	80 ± 29	0.070
HDL, mg/dl	45 ± 12	59 ± 44	0.142
SPECT data			
Exercise stress	19 (33)	9 (23)	0.976
Pharmacological stress	39 (67)	30 (77)	0.298
EDV, mL	113 ± 51	118 ± 534	0.667
ESV, mL	57 ± 36	63 ± 40	0.424
LVEF, %	54 ± 14	50 ± 13	0.212
SSS	1.8 ± 4.2	3.5 ± 6.4	0.169
SRS	1.2 ± 3.0	2.3 ± 4.4	0.209
SDS	0.6 ± 1.7	1.2 ± 3.2	0.314
Medical treatment			
ACE-I and/or ARB	14 (24)	11 (28)	0.653
β-blocker	6 (10)	5 (13)	0.706
Vasodilators	4 (7)	9 (23)	0.022
Statin	7 (12)	9 (15)	0.152
Antidiabetic drugs	16 (28)	17 (45)	0.103

All abbreviations as in Table 2.

Results in the group of patients with severe CKD

Comparison of clinical characteristics and stress myocardial perfusion SPECT and QGS parameters between the MACCRE and non-MACCRE groups

The clinical characteristics and scintigraphic parameters of the patients with severe CKD in the MACCRE and non-MACCRE groups are shown in Table 5. Both groups were similar with respect to age, sex, body mass index, hemodialysis rate, and history of hypertension, dyslipidemia, or MI. The prevalence of DM was significantly higher in the MACCRE group than in the non-MACCRE group, but hemoglobin (Hb) and eGFR were significantly lower in the MACCRE group than in the non-MACCRE group.

We found no significant differences between the 2 groups in the data from the perfusion SPECT studies and the frequency of exercise stress or pharmacological stress.

Medication such as vasodilators was used more frequently in the MACCRE group than in the non-MACCRE group.

Univariate Cox proportional hazards models for MACCRE

The results of univariate Cox proportional hazards analysis of factors related to MACCRE in patients with severe CKD are displayed in Table 6. The significant clinical factors were DM, Hb, eGFR, and low-density lipoproteins. With respect to pharmacotherapy, vasodilators were a significant factor.

Multivariate Cox analysis of MACCRE

The significant predictors of MACCRE in patients with severe CKD found by multivariate Cox analysis are listed in Table 7. According to the multivariate analysis, the most significant predictors of MACCRE in patients with severe CKD were DM ($P=0.023$, HR=2.161) and eGFR ($P=0.03$, HR=0.954).

Table 6 Univariate Cox proportional hazards analysis for MACCRE in severe CKD patients (eGFR<30 mL/min/1.73 m²)

Variate	Hazard ratio	95% CI	P Value
Age, years	0.999	0.968-1.033	0.943
Male gender	1.048	0.549-2.105	0.890
BMI, kg/m ²	1.043	0.952-1.135	0.357
Hemodialysis	1.268	0.674-2.392	0.459
Hypertension	0.974	0.439-2.581	0.953
Diabetes mellitus	1.990	1.049-3.792	0.036
Dyslipidemia	1.359	0.711-2.551	0.347
Prior MI	1.680	0.574-3.919	0.313
Hb, g/dl	0.829	0.682-1.002	0.053
HbA1c, %	1.248	0.910-1.648	0.161
eGFR, mL/min/1.73 m ²	0.952	0.907-0.993	0.019
TG, mg/dl	0.998	0.992-1.001	0.263
LDL, mg/dl	0.996	0.973-0.999	0.035
HDL, mg/dl	1.009	0.998-1.016	0.105
SPECT data			
Exercise stress	0.686	0.307-1.386	0.305
Pharmacological stress	1.459	0.721-3.262	0.305
EDV, mL	1.001	0.995-1.008	0.583
ESV, mL	1.004	0.996-1.013	0.310
LVEF, %	0.985	0.966-1.007	0.180
SSS	1.045	0.986-1.098	0.132
SRS	1.050	0.968-1.124	0.221
SDS	1.083	0.954-1.184	0.190
Medical treatment			
ACE-I and/or ARB	1.044	0.498-0.958	0.904
β -blocker	1.310	0.449-3.059	0.586
Vasodilators	2.646	1.177-5.388	0.021
Statin	1.297	0.489-2.879	0.570
Antidiabetic drugs	1.742	10.906-3.299	0.095

All abbreviations as in Table 2.

Table 7 Significant predictors for MACCRE by Cox multivariate analysis (eGFR<30 mL/min/1.73 m²)

Variate	Hazard ratio	95% CI	P Value
Diabetes mellitus	2.161	1.115-4.191	0.023
eGFR mL/min/1.73 m ²	0.954	0.908-0.996	0.030
Hb, g/dl	0.831	0.684-1.006	0.058

All abbreviations as in Table 2.

MACCRE-free survival rate

Figure 4 and 5 shows Kaplan-Meier curves for MACCRE-free survival in patients with severe CKD after 2 years of follow-up. Figure 4 shows an event-free rate of 0.74 in the group without DM and 0.59 in the group with DM ($P=0.03$, log-rank test). Figure 5 shows an event-free rate of 0.83 in the group with an eGFR equal to or greater than 15 and of 0.49 in

the group with an eGFR less than 15 ($P=0.005$, log-rank test).

Discussion

The present study aimed to compare differences in prognostic markers for MACCRE between patients with mild and severe CKD. During the 2-year follow-up of 281 patients with CKD, including 44 patients on hemodialysis, MACCRE occurred in 52 of the patients with mild CKD and 39 patients of patients with severe CKD.

Multivariate Cox analysis showed that SDS and ESV were significantly associated with MACCRE in patients with mild CKD, and DM and eGFR were significantly associated with MACCRE in patients with severe CKD. On the basis of a large-scale prospective multicenter trial (Japanese Assessment of Cardiac Events and Survival Study, J-ACCESS), Nishimura et al. reported that stress myocardial perfusion SPECT was a

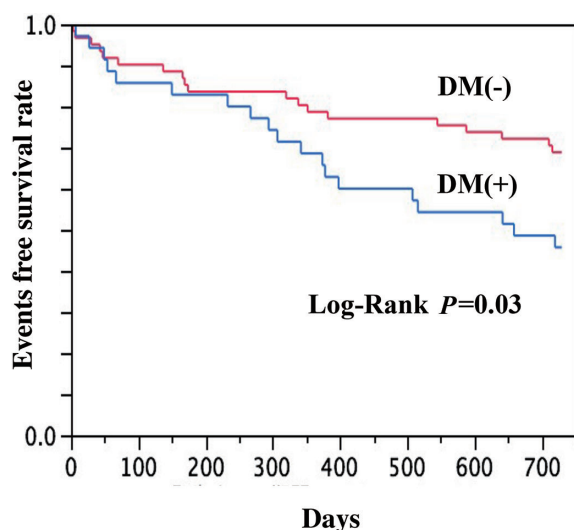


Figure 4 Influence of DM on the 2-year event-free rate for major adverse cardiac, cerebrovascular, and renal events in patients with chronic kidney disease.

useful prognostic tool for patients with suspected or confirmed ischemic heart disease (15). In addition, subanalysis of the J-ACCESS database revealed a relationship between major cardiac events and perfusion SPECT findings in patients with CKD (18, 19).

Although this J-ACCESS subanalysis demonstrated that SPECT had incremental value for predicting cardiac events (18,19), the study population did not include patients with end-stage renal disease requiring hemodialysis and was similar to our population of patients with mild CKD. On the other hand, several studies have reported that stress myocardial perfusion SPECT is useful for detecting ischemic heart disease and predicting cardiac events in hemodialysis patients (16, 20, 21); the population of those studies was similar to our population of patients with severe CKD.

Little is known about the prognostic value of stress myocardial perfusion SPECT for patients in all stages of CKD, including those on hemodialysis and those being conservatively managed for kidney dysfunction. Furthermore, no reports compared patients with mild and severe CKD, including patients on hemodialysis.

In the present study, SDS was a significant predictor of MACCRE in patients with mild CKD. In mild CKD patients, 56% of MACCRE was occupied by revascularization, which was connected with the myocardial ischemia. As a result, MACCRE-free survival rate was considered to be higher in an SDS under 4 than an SDS greater than or equal to 4.

In previous studies that included revascularization or unstable angina pectoris as endpoints, multivariate Cox analysis also showed that SDS was one of the significant independent variables for predicting major cardiac events in patients with CKD (16, 21, 22, 24, 25).

The main reason for performing SPECT is to evaluate

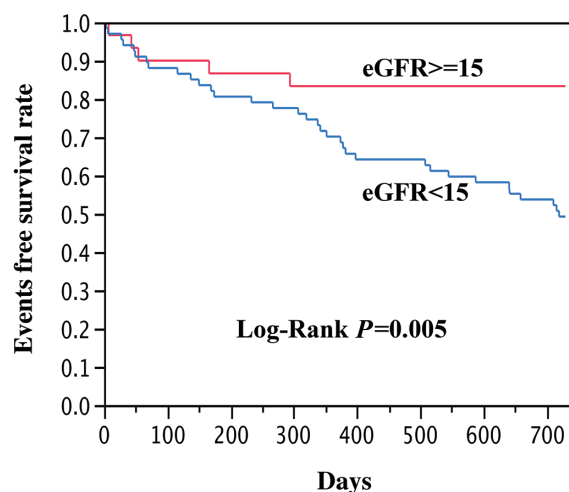


Figure 5 Influence of eGFR on the 2-year event-free rate for major adverse cardiac, cerebrovascular, and renal events in patients with chronic kidney disease.

myocardial ischemia, and the SDS indicates the severity of myocardial ischemia. Two studies, the COURAGE and FAME studies, reported on the importance of imaging procedures for predicting the outcome of myocardial ischemia (26, 27). In the COURAGE nuclear substudy (26), the event-free survival rate in patients with a reduction in ischemic volume of 5% or more evaluated by SPECT was significantly better than in patients with a reduction of less than 5%, even though patients with coronary artery disease (CAD) were treated by optimal therapy or percutaneous coronary intervention (PCI). The FAME study (27) evaluated myocardial ischemia by fractional flow reserve (FFR) during coronary angiography in patients with multivessel CAD and found that the event-free survival rate in patients who underwent FFR-guided PCI (ie, MI-guided PCI) was significantly better than in patients who underwent angiography-guided PCI. However, FFR is not easier to perform than SPECT. In our study, myocardial ischemia was also an important predictor of MACCRE in patients with mild CKD with suspected ischemic heart disease, indicating that SPECT can provide useful prognostic information in these patients.

ESV was another significant predictor of MACCRE in patients with mild CKD. The importance of ESV was reported in some studies (15, 28, 29). In a study in 4,031 patients with suspected or confirmed ischemic heart disease, Nishimura et al. reported that multivariate Cox analysis identified ESV as one of the most important predictors of cardiac events (including cardiac death, nonfatal MI, and severe heart failure) (15). Subanalysis of this study showed that according to multivariate Cox analysis ESV was also one of the significant predictors in patients with CKD (18).

In our study, DM was one of the main factors that influenced the incidence of cardiovascular, cerebrovascular,

and renal events in patients with severe CKD. This finding is in line with previous studies that also found that DM was one of the important predictors of major cardiac events (15, 18, 22, 30). The same is true for eGFR, which in our study was a significant predictive factor of MACCRE in patients with severe CKD and in previous studies was a significant independent predictor of major cardiac events (18, 22, 23).

Revascularization is an event that is related to myocardial ischemia. In our study, revascularization was significantly lower in patients with severe CKD than in patients with mild CKD. On the other hand, hospitalization for heart failure and renal events were significantly higher in patients with severe CKD than in patients with mild CKD. Those factors affected our results that eGFR and DM were significant predictors in patients with severe CKD. However, there were some previous studies that the parameters for myocardial SPECT were useful in patients with end-stage CKD. Momose et al. reported that SDS is a strong predictor for asymptomatic diabetic CKD patients who initiated hemodialysis (16). Hase et al. reported that myocardial perfusion defect was independent predictor in patients with end-stage renal disease (21).

In general, the initiation of hemodialysis decreases quality of life and increases the physical and mental burden on patients, and patients on maintenance hemodialysis have a high mortality rate (16, 21). Therefore, we devised MACCRE as an original endpoint for this study.

Several limitations of this study need to be considered. First, an inclusion criterion was an eGFR below 60 mL/min/1.73 m², and we did not assess control data from the general population or from patients with an eGFR greater than 60 mL/min/1.73 m². Therefore, we could not compare the value of myocardial perfusion SPECT in predicting cardiac events in patients with and without CKD. Second, the number of patients included in our study was relatively small compared with previous studies (22, 30). Further prospective investigations in a larger group of patients with CKD, including patients on hemodialysis, will be necessary to better evaluate the relations of myocardial perfusion SPECT parameters to mortality and morbidity in patients with CKD, including patients on hemodialysis.

Conclusions

Multivariate Cox analysis showed that SDS and ESV were significant predictors of MACCRE in patients with mild CKD, whereas DM and eGFR as well as myocardial perfusion SPECT parameters were significant predictors of MACCRE in patients with severe CKD. Thus, predictors of MACCRE differ between patients with mild and those with severe CKD.

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Conflicts of interest

The authors have no conflicts of interest to declare in relation to this article.

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