


Predictive impacts of chronic kidney disease and cardiac sympathetic nervous activity on lethal arrhythmic events in chronic heart failure

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None.

Abstract

Background: The clinical implications of chronic kidney disease (CKD) and cardiac sympathetic nervous activity (CSNA) regarding lethal arrhythmic events have not yet been fully elucidated in patients with chronic heart failure (CHF). We hypothesized that the combination of CKD and abnormal CSNA, assessed by ¹²³I-metaiodobenzylguanidine (¹²³I-MIBG) scintigraphy, may provide useful prognostic information for lethal arrhythmic events.

Methods: We studied 165 consecutive hospitalized CHF patients without dialysis. Cardiac ¹²³I-MIBG scintigraphy was performed in a clinically stable condition, and abnormal CSNA was defined as a late heart-to-mediastinum ratio of <1.6. CKD was defined as an estimated glomerular filtration rate of <60 ml/min/1.73 m². We then investigated the incidence of lethal arrhythmic events (sustained ventricular tachyarrhythmia, appropriate implantable cardioverter-defibrillator therapy, or sudden cardiac death).

Results: During a median follow-up of 5.3 years, lethal arrhythmic events were observed in 40 patients (24.2%). The patients were divided into four groups according to the presence of CKD and CSNA abnormality: non-CKD/normal CSNA ($n = 52$), CKD/normal CSNA ($n = 39$), non-CKD/abnormal CSNA ($n = 33$), and CKD/abnormal CSNA ($n = 41$). Kaplan–Meier analysis showed that CKD/abnormal CSNA had the highest event rate (log-rank $p = .004$). Additionally, the Cox proportional hazard analysis revealed that CKD/abnormal CSNA was a predictor for lethal arrhythmic events compared with non-CKD/normal CSNA (hazard ratio, 5.368, $p = .001$). However, the other two groups did not show significant differences compared with the non-CKD/normal CSNA group.

Conclusions: The combination of CKD and abnormal CSNA, assessed by ¹²³I-MIBG scintigraphy, had a high predictive value for lethal arrhythmic events in patients with CHF.

KEYWORDS

¹²³I-metaiodobenzylguanidine scintigraphy, cardiac sympathetic nervous activity, chronic kidney disease, sudden cardiac death, ventricular tachyarrhythmia

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1 | INTRODUCTION

Chronic kidney disease (CKD) is an important comorbidity for the incidence of cardiovascular events such as worsening of heart failure, atrial fibrillation (AF), and ischemic heart disease in patients with chronic heart failure (CHF). (Gansevoort et al., 2013) It is well known that dialyzed patients with end-stage kidney disease have a high risk of lethal arrhythmic events such as sustained ventricular tachyarrhythmia and sudden cardiac death. (Karnik et al., 2001) However, the relationship between CKD and incidence of lethal arrhythmic events has not yet been fully elucidated in CHF patients without dialysis. Cardiac sympathetic nervous activity (CSNA) plays an important key role in the pathogenesis of cardiorenal syndrome, (Cao et al., 2000; Zoccali et al., 2002) and abnormal CSNA is generally considered to be associated with the incidence of lethal arrhythmic events. (Cao et al., 2000) We thus hypothesized that the combination of CKD and abnormal CSNA leads to a higher incidence of lethal arrhythmic events in CHF patients without dialysis.

In patients with CHF, it is not simple to assess CSNA abnormality and ventricular arrhythmogenicity because of high prevalence of CKD and AF as comorbidity of heart failure. Recently, the utility of late gadolinium enhancement on magnetic resonance imaging has been established for arrhythmic risk stratification; (Muser et al., 2021) however, the use of gadolinium-based contrast agents is sometimes difficult for patients with CKD. Additionally, the assessment of heart rate variability, which represents CSNA, (Sassi et al., 2015) is also difficult due to the lack of reliable data analysis for patients with AF or cardiac implantable electronic devices. On the other hand, cardiac ^{123}I -metaiodobenzylguanidine (MIBG) scintigraphy enables us to assess CSNA regardless of renal function and patient heart rhythm. (Jacobson et al., 2010; Mabuchi et al., 2005; Verberne et al., 2011) Therefore, the aim of our study was to clarify the clinical implication of CKD and abnormal CSNA, assessed by ^{123}I -MIBG scintigraphy, for lethal arrhythmic events in CHF patients without dialysis.

2 | MATERIALS AND METHODS

2.1 | Study population

The present study retrospectively enrolled 170 consecutive patients who were hospitalized for therapy of HF and underwent cardiac ^{123}I -MIBG scintigraphy at Fukushima Medical University Hospital between 2010 and 2018. The clinical characteristics of the study population are listed in Table 1. The diagnosis of heart failure was made by several cardiologists, based on the established guidelines. (Ponikowski et al., 2016) All patients received optimal medication and were in stable condition with New York Heart Association (NYHA) class I/II on cardiac ^{123}I -MIBG scintigraphy examination. Blood examination and echocardiography were also performed with each patient in a stable condition before discharge. Several patients

TABLE 1 Baseline characteristics of the study subjects

N	165
Age (years)	59.8 ± 16.0
Male (n, %)	117 (70.9%)
Hypertension (n, %)	117 (70.9%)
Diabetes (n, %)	79 (47.9%)
Dyslipidemia (n, %)	121 (73.3%)
Chronic kidney disease (n, %)	80 (48.5%)
Anemia (n, %)	67 (40.6%)
Ischemic heart disease etiology (n, %)	31 (18.8%)
Atrial fibrillation (n, %)	54 (32.7%)
Past ICD implantation at enrollment (n, %)	13 (7.8%)
Medication	
β-Blockers (n, %)	149 (90.3%)
ACE inhibitors/ARBs (n, %)	144 (87.3%)
Amiodarone (n, %)	27 (16.4%)
Diuretics (n, %)	115 (69.7%)
Inotropic agents (n, %)	46 (27.9%)
Laboratory data	
BNP (pg/ml)	220.7 (69.5–533)
eGFR (ml/min/1.73 m ²)	65.0 ± 24.4
Echocardiography	
LVEF (%)	34.8 (26.0–50.7)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction.

who received maintenance dialysis ($n = 5$) were excluded. The remaining 165 patients constituted the final study population. Written informed consent was obtained from all study subjects, and the study protocol was approved by the Ethics Committee of Fukushima Medical University.

2.2 | Definition of CKD and CSNA

The definition of CKD was an estimated glomerular filtration rate (eGFR) of <60 ml/min/1.73 m². (Levey et al., 2006) The measurement of eGFR was performed based on the Modification of Diet in Renal Disease formula. (Levey et al., 2006) In the present study, CSNA was assessed by ^{123}I -MIBG scintigraphy, and abnormal CSNA was defined as a late heart-to-mediastinum ratio (HMR) of <1.6 based on the AdreView Myocardial Imaging for Risk Evaluation in Heart Failure (ADMIRE-HF) trial. (Jacobson et al., 2010) The patients were then divided into four groups according to the presence of CKD and CSNA abnormality: non-CKD/normal CSNA ($n = 52$), CKD/normal CSNA ($n = 39$), non-CKD/abnormal CSNA ($n = 33$), and CKD/abnormal CSNA ($n = 41$).

2.3 | ^{123}I -MIBG scintigraphy protocol

The protocol of ^{123}I -MIBG scintigraphy was decided as described in previous articles. (Flotats et al., 2010; Nakajima & Nakata, 2015) ^{123}I -MIBG scans were performed 20 min (early) and 3.5 h (late) after the tracer injection. The dose of ^{123}I -MIBG was 111 MBq, which is the lowest dose of recommended dose in the United States and Europe (111–370 MBq); (Flotats et al., 2010) however, it is generally the administered dose in Japan. (Nakajima & Nakata, 2015) A planar image was obtained from an anterior view for 5 min with an energy window centered at 159 keV and a window width of 15% by the single photon emission computed tomography device (GCA-9300A, TOSHIBA Co., Ltd). A low-energy high-resolution collimator was used in our study. For calculating the HMR and wash out rate, the region of interest was positioned semiautomatically utilizing smartMIBG software (Fujifilm RI Pharma Co., Ltd) by an experienced nuclear medicine technician who was blind to the clinical data. The results of the ^{123}I -MIBG scintigraphy were interpreted by independent cardiologists.

2.4 | Echocardiography

Echocardiography was performed by experienced echocardiographers using standard techniques with an ultrasound system at Fukushima Medical University Hospital. (Yamada et al., 2018) Interventricular septum thickness, posterior wall thickness, and left ventricular (LV) end-diastolic diameter were measured in the parasternal long-axis view at end diastole, and LV end-systolic diameter was measured in the same view at end systole. LV ejection fraction, LV end-diastolic volume index, LV end-systolic volume index, and left atrial volume index were calculated using the modified Simpson's method.

2.5 | Definition of other clinical risk factors

Clinical risk factors except for CKD were defined as the following. The definition of hypertension was the recent use of antihypertensive medications, a systolic blood pressure of ≥ 140 mm Hg, and/or a diastolic blood pressure of ≥ 90 mm Hg. (Mancia et al., 2013) The definition of diabetes was the recent use of antidiabetic medications (insulin or antidiabetic drugs), a fasting blood glucose value of ≥ 126 mg/dl, and/or hemoglobin A_{1c} value of $\geq 6.5\%$. (American Diabetes Association, 2014) The definition of dyslipidemia was the recent use of cholesterol-lowering medications, a triglyceride value of ≥ 150 mg/dl, a low-density lipoprotein cholesterol value of ≥ 140 mg/dl, and/or a high-density lipoprotein cholesterol value of < 40 mg/dl. (Teramoto et al., 2013) The definition of anemia was a hemoglobin level of < 13 g/dl in men and < 12 g/dl in women. (Beutler & Waalen, 2006) Ischemic heart disease was defined as history of myocardial infarction or angina pectoris, or heart failure with

coronary artery stenosis, which needed percutaneous or surgical intervention.

2.6 | Follow-up and event ascertainment

All patients were followed up on until December 2020. A lethal arrhythmic event was defined as sustained ventricular tachyarrhythmia requiring electrical cardioversion or defibrillation, appropriate implantable cardioverter-defibrillator (ICD) therapy (anti-tachycardia pacing or shock therapy), or sudden cardiac death. Before and after study enrollment, implantation of ICD or cardiac resynchronization therapy with defibrillator (CRT-D) was performed in accordance with the established criteria. (Epstein et al., 2008) Programming of ICD therapy was performed at the cardiologist's discretion according to the patient's background. The definition of sudden cardiac death was the unexpected death of an individual not attributable to an extracardiac cause, within one hour of symptom onset. (Zipes & Wellens, 1998) Dates of arrhythmic event were obtained from patient's medical records or their referring cardiologists. Survival time was calculated from the date of assessment of CSNA with cardiac ^{123}I -MIBG scintigraphy until the date of incidence of lethal arrhythmic event or the date of last follow-up. In the present study, clinical characteristics and the incidence of lethal arrhythmic events were compared among the four groups.

2.7 | Statistical analysis

Normally distributed data are presented as mean \pm standard deviation (SD). Non-normally distributed data are reported as median and interquartile range. Categorical variables are expressed as numbers and percentages. Differences among the four groups were assessed utilizing analysis of variance for comparison of parametric continuous variables, the Kruskal-Wallis test for comparison of non-parametric continuous variables, and the chi-square test for comparison of categorical variables. The Cox proportional hazards regression analysis was performed to clarify the relationship of CKD and abnormal CSNA to the incidence of arrhythmic events. The cumulative incidence curve of arrhythmic events was plotted via the Kaplan-Meier analysis, with statistical significance examined utilizing the log-rank test. In addition, the relative excess risk due to interaction about the incidence of arrhythmic event was calculated to investigate whether there was an additive interaction between CKD and abnormal CSNA. It has been reported that relative excess risk due to interaction is the excess risk as a result of joint exposure. (Knol et al., 2011) In the present study, it was calculated by subtracting the sum of hazard ratios of CKD/normal CSNA group and non-CKD/abnormal CSNA group from the hazard ratio of CKD/abnormal CSNA group plus 1.0. Relative excess risk due to interaction > 0 means positive or additive interaction. (Knol et al., 2011) A value of $p < .05$ was considered statistically significant. Statistical analyses were performed with the statistical software SPSS 26.0 (IBM Corp.).

3 | RESULTS

3.1 | Baseline characteristics

The baseline characteristics of the study subjects are shown in Table 1. The study subjects ($n = 165$) were divided into four groups based on presence of CKD and CSNA abnormality: non-CKD/normal CSNA ($n = 52$), CKD/normal CSNA ($n = 39$), non-CKD/abnormal CSNA ($n = 33$), and CKD/abnormal CSNA ($n = 41$). As shown in Table 2, patients in the CKD/abnormal CSNA group were more likely to be older and had higher prevalence of diabetes, dyslipidemia, anemia and intake of amiodarone, diuretics, and inotropic agents. Regarding laboratory data, the patients in the CKD/abnormal CSNA group had higher levels of B-type natriuretic peptide, creatinine, and high-sensitivity C-reactive protein, as well as lower levels of eGFR, potassium, sodium, and albumin. As for echocardiography, the patients in the CKD/abnormal CSNA group had lower LV ejection fraction and higher LV end-systolic volume index and LV end-systolic diameter. With respect to the prevalence of AF, the patients in the non-CKD/normal CSNA group had lower prevalence rate. Regarding the ^{123}I -MIBG scintigraphy data, the patients in the CKD/abnormal CSNA group had lower early HMR, lower late HMR, and higher washout rate.

3.2 | ICD or CRT-D implantation

At study enrollment, ICD implantation rates did not differ among the four groups (Table 2). During the follow-up period, ICD was implanted in 12 (7.3%) patients and CRT-D was implanted in 20 (12.1%) patients for primary prevention based on the established criteria. (Epstein et al., 2008) By the time the clinical endpoints occurred, the number of patients who received ICD or CRT-D implantation was 9 (13.5%) of the non-CKD/normal CSNA, 8 (10.3%) of CKD/normal CSNA, 10 (24.2%) of non-CKD/abnormal CSNA, and 18 (31.7%) of CKD/abnormal CSNA. Patients in the CKD/abnormal CSNA group had higher ICD or CRT-D implantation rate ($p = .025$).

3.3 | Predictive impact of the combination of CKD and abnormal CSNA on lethal arrhythmic events

During a median follow-up period of 5.3 years, there were 40 (24.2%) lethal arrhythmic events (8 sustained ventricular tachyarrhythmias, 21 appropriate ICD therapies, and 11 sudden cardiac deaths). Arrhythmic events occurred in 5 (9.6%) of the non-CKD/normal CSNA patients, 10 (25.6%) of the CKD/normal CSNA, 9 (27.3%) of the non-CKD/abnormal CSNA, and 16 (39.0%) of the CKD/abnormal CSNA ($p = .011$). As shown in Figure 1, the Kaplan-Meier analysis showed that the CKD/abnormal CSNA group had the highest lethal arrhythmic event rate (log-rank $p = .004$). The Cox proportional hazard analysis showed that CKD/abnormal CSNA was a predictor for lethal arrhythmic events compared with non-CKD/

normal CSNA (hazard ratio, 5.368 [95% confidence interval, 1.955–14.743], $p = .001$), as shown in Table 3. However, the CKD/normal CSNA and non-CKD/abnormal CSNA groups did not show significant differences in the incidence of lethal arrhythmic events compared with the non-CKD/normal CSNA group. The relative excess risk due to interaction for the combination of CKD and abnormal CSNA was 1.244, suggesting an increase in risk of lethal arrhythmic events due to additive interaction of the two categories.

4 | DISCUSSION

In the present study, patients with both CKD and abnormal CSNA had the highest arrhythmic event rate during the long follow-up period, and the combination of CKD and abnormal CSNA was a predictive factor for lethal arrhythmic events. However, either CKD or abnormal CSNA alone was not significantly associated with arrhythmic events. These results indicate that the assessment of both renal function and CSNA using ^{123}I -MIBG scintigraphy provides useful information for arrhythmic risk stratification in CHF patients without dialysis.

4.1 | Clinical value of combination of CKD and abnormal CSNA for prediction of lethal arrhythmic events

Chronic kidney disease is a well-known risk factor for the development of cardiovascular disease, which leads to poor prognosis. (Gansevoort et al., 2013) In addition, it has been demonstrated that dialyzed patients with end-stage kidney disease have a high risk of ventricular tachyarrhythmia or sudden cardiac death. (Karnik et al., 2001) However, most clinical heart failure studies exclude patients with CKD and do not provide adequate information on the risk stratification for major adverse cardiac events in CHF patients with CKD. Therefore, there is a lack of evidence about the relationship between CKD and lethal arrhythmic events in non-dialyzed CHF patients with CKD. CSNA is considered one of the pathophysiological mechanisms underlying the development of cardiorenal syndrome in patients with CKD. (Cao et al., 2000; Zoccali et al., 2002) and abnormal CSNA is associated with the incidence of ventricular tachyarrhythmias. (Cao et al., 2000) Therefore, we hypothesized that CHF patients with both CKD and abnormal CSNA have an increased risk of lethal arrhythmic events. To prove this hypothesis, we assessed the clinical implications of CKD and abnormal CSNA for sustained ventricular tachyarrhythmia or sudden cardiac death. Consequently, we clearly demonstrated that the combination of CKD and abnormal CSNA had a high predictive value for the incidence of lethal arrhythmic events in patients with CHF. In the present study, patients with both CKD and abnormal CSNA had higher prevalence of anemia, diabetes and intake of diuretics, higher levels of B-type natriuretic peptide, high-sensitivity C-reactive protein, lower levels of potassium, and lower LV ejection fraction, compared with the other patients. These cardiovascular risk factors are highly prevalent in patients with CHF, and they contribute

TABLE 2 Comparison of clinical factors among the four groups

	Non-CKD/normal CSNA (n = 52)	CKD/normal CSNA (n = 39)	Non-CKD/abnormal CSNA (n = 33)	CKD/abnormal CSNA (n = 41)	p value
Age (years)	54.5 ± 17.8	66.3 ± 12.2	58.0 ± 15.8	61.7 ± 15.1	.004
Male (n, %)	34 (65.4%)	27 (69.2%)	21 (63.6%)	35 (85.4%)	.121
Hypertension (n, %)	34 (65.4%)	31 (79.5%)	21 (63.6%)	31 (75.6%)	.328
Diabetes (n, %)	13 (25.0%)	21 (53.8%)	19 (57.6%)	26 (63.4%)	.001
Dyslipidemia (n, %)	32 (61.5%)	32 (82.1%)	21 (63.6%)	36 (87.8%)	.011
Anemia (n, %)	16 (30.8%)	18 (46.2%)	9 (27.3%)	24 (58.5%)	.015
Ischemic heart disease (n, %)	6 (11.5%)	11 (28.2%)	5 (15.2%)	9 (22.0%)	.202
Atrial fibrillation (n, %)	8 (15.4%)	19 (48.7%)	10 (30.3%)	17 (41.5%)	.004
ICD implantation at enrollment (n, %)	2 (3.8%)	4 (10.3%)	2 (6.1%)	5 (12.2%)	.445
Medications					
β-Blockers (n, %)	43 (82.7%)	36 (92.3%)	31 (93.9%)	39 (95.1%)	.157
ACE inhibitors/ARBs (n, %)	42 (80.7%)	32 (82.1%)	32 (97.0%)	38 (92.7%)	.078
Amiodarone (n, %)	2 (3.8%)	5 (12.8%)	4 (12.1%)	16 (39.0%)	<.001
Diuretics (n, %)	27 (51.9%)	24 (61.5%)	27 (81.8%)	37 (90.2%)	<.001
Inotropic agents (n, %)	7 (13.5%)	8 (20.5%)	12 (36.4%)	19 (46.3%)	.002
Laboratory data					
Albumin (g/dl)	3.9 ± 0.5	3.6 ± 0.6	3.7 ± 0.5	3.5 ± 0.5	.002
Sodium (mmol/l)	140.4 ± 2.5	139.8 ± 2.3	138.2 ± 2.8	138.0 ± 3.1	<.001
eGFR (ml/min/1.73 m ²)	82.6 ± 23.0	50.5 ± 17.8	73.7 ± 16.1	49.5 ± 18.5	<.001
Blood urea nitrogen (mg/dl)	14.0 (11.0–18.5)	21.0 (17.0–27.0)	15.0 (13.0–17.0)	20.0 (16.0–26.5)	<.001
Creatinine (mg/dl)	0.7 (0.7–0.8)	1.1 (0.9–1.4)	0.8 (0.7–0.9)	1.2 (1.0–1.4)	<.001
Potassium (mmol/l)	4.2 (4.0–4.5)	4.4 (4.1–4.7)	4.1 (3.9–4.3)	4.1 (3.8–4.7)	.031
BNP (pg/ml)	109.2 (38.4–221.3)	205.1 (77.5–439.0)	231.8 (69.9–442.7)	519.6 (218.8–875.8)	<.001
hs-CRP (mg/dl)	0.2 (0.1–0.5)	0.2 (0.1–1.2)	0.2 (0.1–0.6)	0.5 (0.2–1.3)	.045
Echocardiography					
LVEF (%)	38.5 (26.5–56.9)	43.2 (31.5–55.0)	39.0 (24.3–50.4)	29.1 (25.0–37.0)	.004
LVEDVI (ml/m ²)	77.5 ± 32.4	75.5 ± 38.7	89.6 ± 38.7	90.4 ± 43.8	.180
LVESVI (ml/m ²)	48.1 ± 29.9	44.0 ± 29.1	58.8 ± 33.7	63.8 ± 39.1	.030
Left atrial volume index (ml/m ²)	39.0 ± 22.4	54.6 ± 33.8	48.3 ± 31.0	51.3 ± 19.8	.050
LV end-diastolic diameter (mm)	56.0 ± 10.6	55.5 ± 9.4	57.3 ± 10.2	60.7 ± 10.6	.087
LV end-systolic diameter (mm)	43.9 ± 14.3	43.6 ± 11.5	46.8 ± 11.6	51.3 ± 11.8	.018
IVS thickness (mm)	10.6 ± 2.9	11.3 ± 3.4	10.7 ± 2.7	10.2 ± 2.5	.326
Posterior wall thickness (mm)	10.5 ± 2.2	11.4 ± 2.8	10.8 ± 2.0	10.5 ± 2.0	.232
¹²³I-MIBG scintigraphy					
Early HMR	2.1 ± 0.3	2.0 ± 0.2	1.6 ± 0.2	1.6 ± 0.2	<.001
Late HMR	2.0 ± 0.3	1.9 ± 0.2	1.4 ± 0.1	1.4 ± 0.2	<.001
WOR (%)	24.8 ± 11.2	24.7 ± 12.1	48.6 ± 14.3	48.6 ± 16.3	<.001

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BNP, brain natriuretic peptide; CKD, chronic kidney disease; CSNA, cardiac sympathetic nervous activity; eGFR, estimated glomerular filtration rate; HMR, heart-to-mediastinum ratio; hs-CRP, high-sensitivity C-reactive protein; ICD, implantable cardioverter-defibrillator; IVS, interventricular septum; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume index; MIBG, metaiodobenzylguanidine; WOR, washout rate.

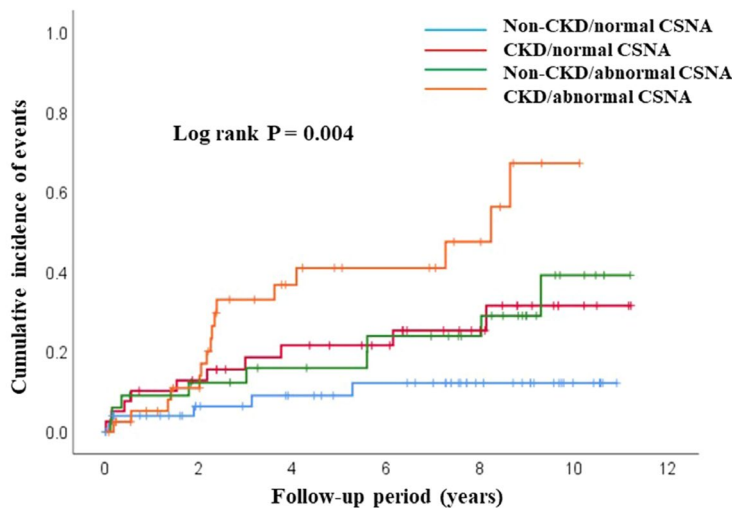


FIGURE 1 The cumulative incidence curve with log-rank test among four groups. Study subjects were divided into four groups based on presence of CKD (eGFR <60ml/min/1.73m²) and abnormal CSNA (late HMR <1.6): non-CKD/normal CSNA (*n* = 52), CKD/normal CSNA (*n* = 39), non-CKD/abnormal CSNA (*n* = 33), and CKD/abnormal CSNA (*n* = 41). Abbreviations: CKD, chronic kidney disease; CSNA, cardiac sympathetic nervous activity; HMR, heart-to-mediastinum ratio; eGFR, estimated glomerular filtration rate

No. at Risk

	0	2	4	6	8	10	12
Non-CKD/normal CSNA	52	37	32	28	17	6	
CKD/normal CSNA	39	32	26	22	14	4	
Non-CKD/abnormal CSNA	33	26	22	19	15	4	
CKD/abnormal CSNA	41	30	15	11	7	1	

Lethal arrhythmic events (40 events/165 patients)	HR	95% CI	<i>p</i> value
Combination of CKD and abnormal CSNA			
Non-CKD/normal CSNA	Reference	-	-
CKD/normal CSNA	2.543	0.869-7.444	.088
Non-CKD/abnormal CSNA	2.581	0.865-7.704	.089
CKD/abnormal CSNA	5.368	1.955-14.743	.001

TABLE 3 Cox proportional hazard model of lethal arrhythmic events

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; CSNA, cardiac sympathetic nervous activity; HR, hazard ratio.

strongly to the incidence of lethal arrhythmic events. (Cooper et al., 1999; Goldenberg et al., 2017; Macdonald & Struthers, 2004; Scott et al., 2009; Streitner et al., 2009; Vinik & Ziegler, 2007) Therefore, our evidence supports that lethal arrhythmic events were frequently observed in patients with both CKD and abnormal CSNA.

4.2 | Utility of cardiac ¹²³I-MIBG scintigraphy in prediction of lethal arrhythmic events in patients with CHF

It has been generally considered that abnormal CSNA is associated with the progression of heart failure and high cardiac mortality in patients with CHF. (Jacobson et al., 2010) Although heart rate variability is a simple and noninvasive assessment of CSNA, (Liu et al., 2020; Sassi et al., 2015) its utility has not been established for patients with heart rhythm disorder. Since CHF patients with CKD have higher prevalence of AF compared with the general population, (Alonso et al., 2011) the assessment of heart rate variability is not suitable for such patients. On the other hand, ¹²³I-MIBG scintigraphy allows us to assess CSNA even for patients with heart rhythm disorder. (Jacobson et al., 2010; Mabuchi et al., 2005) It has been reported that uptake and storage of MIBG into cardiac sympathetic

neurons act like endogenous neurotransmitter norepinephrine, (Sisson et al., 1987) and damaged cardiac sympathetic neurons in patients with CHF lead to reduced cardiac MIBG retention. In a previous study, (Jacobson et al., 2010) late HMR <1.6 was proposed as a useful predictor of adverse events in patients with CHF. In accordance with the previous report, (Jacobson et al., 2010) we defined abnormal CSNA as late HMR <1.6. Although patients with AF were often excluded from the assessment of the relationship between CSNA and prognosis of heart failure, the present study included 54 (32.7%) patients with AF rhythm. Accordingly, the assessment with cardiac ¹²³I-MIBG scintigraphy was required to adequately investigate the clinical implication of CKD and abnormal CSNA for lethal arrhythmic events in patients with CHF. We therefore clearly showed that patients with both CKD and abnormal CSNA had the highest lethal arrhythmic event rate among patients with CHF.

4.3 | Clinical implications

The present study demonstrated that the assessment of both renal function and CSNA is useful for predicting lethal arrhythmic events in patients with CHF. Although late gadolinium enhancement on magnetic resonance imaging has become a gold standard method to identify

patients at high risk of ventricular tachyarrhythmias, (Muser et al., 2021; Pham et al., 2020) the utility of this method is limited in patients with CKD or cardiac implantable electronic devices. On the other hand, risk assessment with cardiac ^{123}I -MIBG scintigraphy is available and useful for even patients with CKD or cardiac implantable electronic devices. (Jacobson et al., 2010) Our study results indicate that the assessment of both renal function and CSNA using ^{123}I -MIBG scintigraphy allows for adequate prediction of future ventricular tachyarrhythmias.

4.4 | Limitations

First, the current study was performed in a single center, and the number of study population and events were relatively small. Second, we did not follow up on eGFR and late HMR. Finally, we performed a Cox proportional hazard analysis but did not statistically adjust the differences in clinical backgrounds among the four groups, because of small number of events. We are considering performing an additional study on these issues in future.

5 | CONCLUSIONS

The combination of CKD and abnormal CSNA was a predictor of lethal arrhythmic events. These results suggest that the assessment of renal function and CSNA using cardiac ^{123}I -MIBG scintigraphy is useful for the risk stratification of lethal arrhythmic events in CHF patients without dialysis.

INFORMED CONSENT

Written informed consent was obtained from all individual participants included in the study.

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CONFLICT OF INTEREST

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ETHICAL APPROVAL

The study protocol was approved by the Ethics Committee of Fukushima Medical University (approval number: 823).

DATA AVAILABILITY STATEMENT

The findings of the present study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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