CardioRenal Medicine

Cardiorenal Med 2019;9:190–200
DOI: 10.1159/000496064
Received: October 9, 2018
Accepted: December 6, 2018
Published online: March 7, 2019

Original Paper

Grading of Left Ventricular Diastolic Dysfunction with Preserved Systolic Function by the 2016 American Society of Echocardiography/ European Association of Cardiovascular Imaging Recommendations Contributes to Predicting Cardiovascular Events in Hemodialysis Patients

Reiko Toida[a] Tatsunori Toida[b, c] Risa Yamashita[c] Norihiro Komiya[a] Shigehiro Uezono[d] Hiroyuki Komatsu[e] Tetsunori Ishikawa[e] Kazuo Kitamura[e] Yuji Sato[f] Shouichi Fujimoto[b, f]

[a]Department of Cardiology, Chiyoda Hospital, Hyuga City, Japan; [b]Department of Hemovascular Medicine and Artificial Organs, Faculty of Medicine, University of Miyazaki, Miyazaki City, Japan; [c]Department of Internal Medicine, Miyazaki Prefectural Nobeoka Hospital, Nobeoka City, Japan; [d]Department of Nephrology, Chiyoda Hospital, Hyuga City, Japan; [e]Division of Circulatory and Body Fluid Regulation, Department of Internal Medicine, University of Miyazaki, Miyazaki City, Japan; [f]Dialysis Division, University of Miyazaki Hospital, Miyazaki City, Japan

Keywords
Diastolic dysfunction · Hemodialysis · Cardiovascular risk

Abstract
Background: Left ventricular diastolic dysfunction (LVDD) causes heart failure with a preserved left ventricular ejection fraction (LVEF) in the general population. ***Objective:*** To examine the relationships between the LVDD grades of the 2016 American Society of Echocardiography/ European Association of Cardiovascular Imaging (ASE/EACVI) recommendations and several arteriosclerotic parameters and major cardiovascular events (MACE) in hemodialysis patients with preserved LVEF. ***Method:*** Sixty-three prevalent hemodialysis patients (median age [interquartile range], 69 [64–75] years, 31.7% female) with normal systolic function (LVEF >50%) were enrolled. LVDD evaluated by echocardiography at baseline was divided into three groups according to ASE/EACVI recommendations (normal diastolic function [ND], n = 24; intermediate, n = 19; diastolic dysfunction [DD], n = 20). All patients underwent analyses of several arteriosclerotic parameters (carotid intima-media thickness [CIMT], plaque score [PS], ankle brachial index [ABI], and brachial-ankle pulse wave velocity [baPWV]). The presence or absence of postdialysis orthostatic hypotension was assessed in each dialysis session. MACE during the 1-year follow-up period was obtained from medical records. Kaplan-Meier and Cox's regression anal-

Tatsunori Toida, MD, PhD
Department of Hemovascular Medicine and Artificial Organs
Faculty of Medicine, University of Miyazaki
5200 Kihara, Kiyotake, Miyazaki 8891692 (Japan)
E-Mail t.toida@med.miyazaki-u.ac.jp

yses were used to investigate the relationship between LVDD grades and MACE. ***Results:*** Post-dialysis orthostatic hypotension and PS, but not CIMT, ABI, or baPWV, increased proportionally with LVDD grades. Eleven patients developed MACE, including 2 cardiovascular deaths. The Kaplan-Meier analysis showed that MACE frequently occurred in the DD grade (p = 0.002 by the log-rank test). Cox's regression analysis adjusted for potential confounders (age, sex, diabetes, systolic blood pressure, and body mass index) revealed that the DD grade was associated with MACE when the ND grade was set as a reference. ***Conclusions:*** In maintenance hemodialysis patients with normal ventricular systolic function, a classification of LVDD by the 2016 ASE/EACVI recommendations may be a useful tool for predicting cardiovascular events.

Introduction

Heart failure (HF) is a common disease in the general population [1], more specifically in patients with chronic kidney disease and end-stage renal disease (ESRD) [2, 3], and is also an important cause of morbidity and mortality. Diastolic HF is defined by the signs and symptoms of HF, along with left ventricular diastolic dysfunction (LVDD) and normal or mildly impaired left ventricular systolic function, called HF with a preserved ejection fraction (HFpEF). HFpEF accounts for one-third to one-half of HF cases in the general population, and its prevalence is steadily increasing [1, 4]. In addition, HFpEF is more common than HF with a reduced ejection fraction (HFrEF) [5]. Morbidity and mortality were previously reported to be higher in patients with diastolic HF than in the general population [1, 5].

LVDD contributes to the development and progression of HFpEF [6]. LVDD and HFpEF are more prevalent than HFrEF in maintenance hemodialysis patients [7]. Previous studies identified diastolic dysfunction (DD), defined as an increased ratio of early mitral flow velocity (E) to early mitral annulus velocity (E') (E/E') and/or a high left atrium volume index, as an independent predictor of mortality in starting and chronic dialysis patients [8–10]. Therefore, echocardiography needs to be employed to confirm cardiovascular risks and guide treatments for ESRD patients on dialysis.

The 2016 American Society of Echocardiography/European Association of Cardiovascular Imaging (ASE/EACVI) recommendations have recently been published [11]. However, their usefulness has not yet been investigated in hemodialysis patients. A recent systemic meta-analysis showed that arterial stiffness and atherosclerosis are related to diastolic function [12], and relationships with several arteriosclerotic parameters: carotid intima-media thickness (CIMT), plaque score (PS), ankle brachial index (ABI), brachial-ankle pulse wave velocity (baPWV), and DD, have been reported in the general population [13, 14]. However, the relationships between the LVDD grades of the ASE/EACVI recommendations and arterial stiffness in hemodialysis patients currently remain unclear.

The aims of the present study were (1) to evaluate LV diastolic function and several atherosclerosis parameters and (2) to investigate the usefulness of the ASE/EACVI recommendations for examining the relationships between LV diastolic function and major cardiovascular events (MACE) in hemodialysis patients with preserved systolic function.

Materials and Methods

Study Design and Subjects

This was a prospective observational study that involved 63 patients who were undergoing maintenance dialysis for ESRD at Chiyoda Hospital, Miyazaki, Japan, and examined carotid artery ultrasonography, echocardiography, and several arteriosclerotic parameters (including ABI and baPWV) between March 2014

and September 2015. Exclusion criteria were as follows: (1) age 20 years or younger, (2) hemodialysis vintage <3 months, (3) ejection fraction (EF) <50%, (4) hypertension that is difficult to control, (5) congestive HF (NYHA cardiac function classification Class III or more severe), (6) atrial fibrillation, (7) severe valvular heart disease, (8) pregnant, lactating, or possibly pregnant women, (9) malignant tumors (including malignant blood tumors), severe infection, systemic blood diseases (such as myelodysplastic syndrome and hemoglobinopathy), hemolytic anemia, and hemorrhagic lesions, including gastrointestinal hemorrhage, and (10) ineligibility judged by the clinical investigator or subinvestigator.

Clinical Data Collection

All patients underwent analyses of several arteriosclerotic parameters (CIMT of the common carotid artery [CCA], PS, ABI, and baPWV). MACE during the 1-year follow-up period was obtained from medical records and was defined as cardiovascular death, sudden death, nonfatal ischemic heart disease, and hospitalization from ischemic or hemorrhagic stroke, causes related to congestive HF, or aortic aneurysm rupture. Sudden death was judged as unexpected death in the first hour following the start of symptoms or when the patient was found dead and had been seen alive 24 h earlier. Stroke was diagnosed using typical imaging and physical findings from examinations. Ischemic heart disease was diagnosed using typical electrocardiogram findings or elevations in myocardium-derived enzymes. Congestive HF was confirmed using electrocardiography, chest radiography, or echocardiography together with the symptoms of dyspnea or edema.

Pre- and postdialysis blood pressure was measured in the supine position. Blood pressure and interdialytic weight gain values were averaged from 3 consecutive HD sessions during the week of patient enrollment. Postdialysis orthostatic hypotension was defined as a reduction in systolic blood pressure of at least 20 mm Hg or diastolic blood pressure of at least 10 mm Hg within 1 min of sitting at least once a week or more. The treatment of hypotension during dialysis was defined as a reduction in or the cessation of ultrafiltration, lifting of the lower limbs, or the use of vasopressors/saline at least once a week or more.

Examination of ABI and PWV

ABI involves measurements of the ratio of blood pressure in the dorsalis pedis or posterior tibial artery to that in the brachial artery without vascular access. baPWV was measured using a volume-plethysmographic apparatus (BP-203RPE III; OMRON Colin Co., Ltd., Tokyo, Japan). Patients rested in the supine position for at least 10 min before the start of monitoring. This apparatus recorded a phonocardiogram, electrocardiogram, and volume pulse form as well as blood pressure at the left or right brachia and ankles without vascular access. baPWV was calculated in a time-phase analysis between the brachial and volume waveforms at the ankles.

Examination of Carotid Artery Ultrasonography

Carotid artery ultrasonography was performed at the time of dry weight after dialysis or on a day that patients did not undergo dialysis. CIMT of CCA and the presence of atherosclerotic plaques were measured using a 7.5-MHz linear probe as a high-resolution transducer and an Aplio XV, Aplio XG, or Xario ultrasonography system (Toshiba Medical Systems Corporation, Tokyo, Japan) using the B mode and a pulsed Doppler system by a single experienced angiologist blinded to clinical information on patients at baseline. Patients were examined in the supine position without a pillow. According to current guidelines, standardized CIMT was measured on the far wall of CCA on a 10-mm segment located 2 cm upstream of the flow divider. Three measurements were performed on the left and right CCA, and the mean values of these measurements were utilized in the analysis.

Carotid PS was calculated using a previously reported method [15]. PS was defined as the sum of the thickest CIMT in individual segments of the bilateral carotid arteries. When assessing PS, plaque length was not considered. Plaques were searched for in the near and far walls of arterial segments by transversal and longitudinal scanning. The mean values of bilateral CIMT and PS measurements were utilized in the analysis.

Echocardiography

Echocardiography was performed at the same time as carotid artery ultrasonography. Comprehensive echocardiographic measurements were performed using an ultrasound machine (Toshiba 270SSA; Toshiba Medical Systems Corporation, Tokyo, Japan) with a 3.75-MHz sector probe by a single experienced cardiologist (R.T.) blinded to clinical information on patients at baseline. All images were obtained with standard techniques using M-mode, two-dimensional, and Doppler measurements in accordance with the ASE/EACVI recommendations [11]. LV systolic function was assessed by calculating the EF using a modified Simpson's

method [16]. LV systolic dysfunction was defined as EF <50%. Pulsed Doppler echocardiography was used to evaluate transmitral LV filling velocities at the tips of the mitral valve. The peak early-diastolic flow velocity (E) and the peak late-diastolic velocity (A) shown as the E/A ratio were measured by analyzing transmitral flow. The ASE/EACVI recommendations showed the four recommended variables for identifying LVDD, and their abnormal cut-off values were annular e' velocity (septal e' <7 cm/s or lateral e' <10 cm/s), average E/e' ratio >14, LA volume index >34 mL/m^2, and peak TR velocity >2.8 m/s. LVDD was normal when more than half of the available variables did not meet the cut-off values for identifying abnormal function. LVDD was present when more than half of the available parameters met these cut-off values, but was indeterminate when only half met these values. Patients were graded as the DD classification in three groups (normal diastolic function [ND], indeterminate [ID], and DD) distributed according to the algorithm for the diagnosis of LVDD in subjects with normal LVEF of the ASE/EACVI recommendations [11].

Statistical Analysis

Descriptive analyses were calculated to describe variables such as patient characteristics in the three groups according to the grades of the DD classification. All continuous variables were presented as medians and interquartile ranges. The Kruskal-Wallis test or χ^2 test was applied for comparisons of the three groups. Crude survival in a group was assessed using a Kaplan-Meier analysis with the log-rank test. Variables that affected MACE ($p < 0.2$) in the univariate analysis were then included in Cox's multivariate proportional hazards models to identify the risk factors associated with MACE. Test results were presented as hazard ratios (HRs) with 95% confidence intervals (CIs), and a p value of <0.05 was considered to be significant. Patients with ND were set as our reference category. All covariates conformed to the proportional hazards model using the Kaplan-Meier method and log-log plot. Receiver operating characteristic curves were computed, and sensitivity analysis of MACE was performed, with the ID group including in the ND (ND + ID vs. DD) or DD (ND vs. ID + DD) group. All statistical analyses were performed with SPSS Statistics 20 (IBM Corp., Armonk, NY, USA).

Ethical Considerations

This observational study was conducted in accordance with the principles contained in the Declaration of Helsinki and was approved by the Chiyoda Hospital Research Ethics Committee (No. 24–1). Data collection was performed in a manner that maintained patient anonymity.

Results

Study Participants and Baseline Characteristics

Sixty-three prevalent hemodialysis patients (median age [interquartile range], 69 [64–75] years, 31.7% female) with normal LV systolic function (EF >50%) were enrolled (Table 1). LV diastolic function evaluated by echocardiography at baseline was divided into three grades according to the ASE/EACVI recommendations (ND group, $n = 24$; ID, $n = 19$; DD, $n = 20$). The predialysis cardiothoracic ratio on chest X-ray was significantly higher in the DD group than in the other groups. Postdialysis orthostatic hypotension increased proportionally with diastolic function grades; 60.0% of the DD group had postdialysis orthostatic hypotension (Table 1). PS increased proportionally with diastolic function grades (ND vs. ID vs. DD, 4.6 [1.6–9.6] vs. 5.6 [2.6–7.0] vs. 8.6 [4.0–10.0]), but not CIMT, ABI, or baPWV (Table 2).

Analysis for MACE

Eleven patients developed MACE including cardiovascular death ($n = 2$), hospitalization for cerebral infarction ($n = 2$), congestive HF ($n = 5$), and nonfatal ischemic heart disease ($n = 2$). The Kaplan-Meier analysis revealed that MACE frequently occurred in the DD group ($p = 0.020$ by the log-rank test) (Fig. 1). Using Cox's proportional hazards model with multicovariate adjustments, age, predialysis systolic blood pressure, previous history of cardiovascular disease, hemoglobin, serum albumin, CIMT, and PS were found to be associated with MACE (Table 3). Cox's regression analysis adjusted for confounders demonstrated that the

CardioRenal Medicine
Cardiorenal Med 2019;9:190–200
DOI: 10.1159/000496064
www.karger.com/crm

Table 1. Baseline characteristics

	All (n = 63)	ND (n = 24)	ID (n = 19)	DD (n = 20)	p value[a]
Age	69.0 (64.0–75.0)	66.5 (62.8–74.0)	72.0 (64.0–77.0)	69.5 (63.3–79.0)	0.422
Male sex, n (%)	43 (68.3)	17 (70.8)	13 (68.4)	13 (65.0)	0.918
Body mass index	20.7 (18.7–23.8)	20.0 (17.9–24.0)	20.9 (19.5–23.0)	19.8 (18.4–24.2)	0.677
IDWG, kg	2.1 (1.5–2.8)	2.2 (1.6–2.7)	1.9 (1.6–2.8)	2.1 (1.1–2.7)	0.850
Dialysis vintage, months	35 (10–83)	45 (14–81)	29 (8–72)	49 (6–110)	0.604
Nonsmoker, n (%)	34 (54.0)	10 (41.7)	11 (57.9)	13 (65.0)	0.278
Daily alcohol consumption, n (%)	3 (4.8)	0 (0.0)	2 (10.5)	1 (5.0)	0.273
Walking independently, n (%)	54 (85.7)	21 (87.5)	16 (84.2)	17 (85.0)	0.948
Dialysis					
Predialysis CTR on chest X-ray, %	51 (47–56)	48 (46–52)	49 (47–53)	57 (51–61)	0.004
Kt/V	1.30 (1.09–1.52)	1.35 (1.16–1.57)	1.20 (0.99–1.51)	1.27 (0.87–1.60)	0.578
Treatment time (more than 4 h), n (%)	55 (87.3)	21 (87.5)	18 (94.7)	16 (80.0)	0.385
AVF, n (%)	57 (90.5)	24 (100.0)	17 (89.5)	16 (80.0)	0.078
Predialysis SBP, mm Hg	158 (143–167)	147 (140–166)	162 (145–179)	158 (148–162)	0.183
Predialysis DBP, mm Hg	74 (71–82)	74 (71–83)	78 (72–82)	73 (67–80)	0.449
Postdialysis SBP, mm Hg	155 (139–173)	150 (137–166)	160 (131–187)	158 (149–170)	0.259
Postdialysis DBP, mm Hg	75 (70–81)	75 (69–81)	77 (74–88)	74 (68–79)	0.209
Postdialysis OH, n (%)	31 (49.2)	8 (33.3)	11 (57.9)	12 (60.0)	0.140
Treatment for hypotension during dialysis, n (%)	21 (33.3)	7 (29.2)	6 (31.6)	8 (40.0)	0.736
Comorbidities					
Previous history of CVD	9 (14.3)	2 (8.3)	2 (10.5)	5 (25.0)	0.248
Diabetes	36 (57.1)	11 (45.8)	13 (68.4)	12 (60.0)	0.316
Medication					
Antihypertensive drug use, n (%)	57 (90.5)	22 (91.7)	17 (89.5)	18 (90.0)	0.967
ESA use, n (%)	57 (90.5)	21 (87.5)	17 (89.5)	19 (95.0)	0.689
Laboratory data					
Hemoglobin, g/dL	10.5 (9.9–11.1)	10.8 (10.5–11.3)	10.5 (10.0–11.1)	10.1 (6.9–10.7)	0.050
Albumin, g/dL	3.5 (3.3–3.8)	3.7 (3.3–3.8)	3.6 (3.3–3.8)	3.4 (3.3–3.6)	0.410
Serum aCa, mg/dL	8.9 (8.6–9.2)	9.1 (8.7–9.3)	8.8 (8.6–9.2)	8.9 (8.7–9.3)	0.873
Serum P, mg/dL	5.1 (4.4–6.2)	5.0 (4.5–6.0)	5.2 (4.4–6.9)	5.3 (4.5–6.3)	0.774

Continuous variables are presented as medians with interquartile ranges in parentheses. ND, normal diastolic function; ID, indeterminate; DD, diastolic dysfunction; IDWG, interdialytic weight gain; CTR, cardiothoracic ratio; AVF, arteriovenous fistula for vascular access; SBP, systolic blood pressure; DBP, diastolic blood pressure; OH, orthostatic hypotension; CVD, cardiovascular disease; ESA, erythropoietin stimulating agents; aCa, adjusted calcium: (4 – serum albumin) + serum calcium if serum albumin <4.0; P, phosphate.[a] By the Kruskal-Wallis test or χ^2 test.

Table 2. Baseline atherosclerosis parameters and cardiac echography

	All (*n* = 63)	ND (*n* = 24)	ID (*n* = 19)	DD (*n* = 20)	*p* value[a]
Atherosclerosis parameters					
CIMT, mm	0.72 (0.62–0.99)	0.73 (0.63–0.93)	0.69 (0.59–0.89)	0.68 (0.55–1.15)	0.839
Plaque score	5.80 (2.30–9.80)	4.55 (1.60–9.60)	5.60 (2.55–7.00)	8.60 (4.00–10.00)	0.125
baPWV, cm/s	1,996.3 (1,688.9–2,420.3)	2,019.5 (1,703.9–2,221.6)	1,965.5 (1,688.3–2,453.8)	1,891.5 (1,700.5–2,512.5)	0.989
ABI	1.18 (1.08–1.30)	1.15 (1.08–1.23)	1.18 (0.95–1.30)	1.20 (1.13–1.33)	0.282
Cardiac echography					
LVEF, %	62.0 (59.0–66.0)	64.5 (60.0–67.8)	64.0 (59.0–65.0)	60.0 (54.0–66.0)	0.216
Lateral E', cm/s	7.6 (6.1–9.7)	8.7 (6.4–11.7)	7.6 (6.6–10.2)	7.1 (4.9–8.2)	0.057
Septal E', cm/s	5.7 (4.8–6.4)	6.3 (5.3–7.2)	5.7 (4.9–6.7)	5.1 (4.2–5.8)	0.006
Average E/e'	11.2 (8.9–15.2)	8.8 (7.2–11.6)	10.1 (9.3–12.9)	15.5 (14.1–18.5)	<0.001
TR velocity, m/s	2.4 (2.0–2.7)	2.2 (2.0–2.5)	2.2 (1.8–2.4)	2.8 (2.4–2.9)	<0.001
LAVI, mL/m^2	33.3 (25.7–48.1)	25.4 (22.7–28.6)	35.6 (26.9–49.7)	48.0 (39.8–75.8)	<0.001

Continuous variables are presented as medians with interquartile ranges in parentheses. ND, normal diastolic function; ID, indeterminate; DD, diastolic dysfunction; CIMT, carotid intima-media thickness; baPWV, brachial-ankle pulse wave velocity; ABI, ankle brachial index; LVEF, left ventricular ejection fraction; E, the peak early-diastolic flow velocity; E', early mitral annulus velocity; TR, tricuspid; LAVI, left atrial volume index. [a] By the Kruskal-Wallis test or χ^2 test.

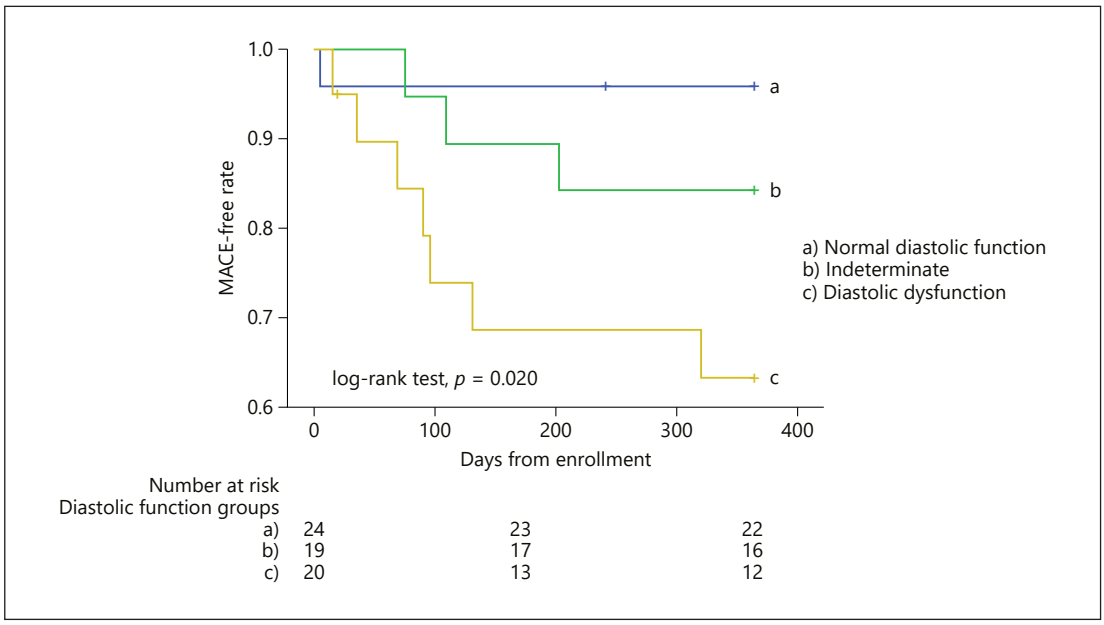

Fig. 1. Kaplan-Meier estimates for major cardiovascular event (MACE)-free rates among baseline diastolic function groups. The survival rate was significantly lower in the diastolic dysfunction group than in the other groups (Kaplan-Meier analysis, log-rank test, $p = 0.020$).

DD group was associated with MACE when the ND group was set as a reference (adjusted HRs 15.99 [95% CI, 1.24–206.05]). Furthermore, in the confounders, PS correlated with MACE (adjusted HRs 1.20 [95% CI, 1.01–1.43]) (Table 3).

Effects of PS on the Relationship between LVDD and MACE

Since DD and PS were identified as risk factors for MACE, we analyzed the effects of PS on the relationship between DD and MACE. When PS was divided into two groups based on the median value, the Kaplan-Meier analysis revealed that MACE frequently occurred in the DD and high PS groups ($p = 0.002$ by the log-rank test). Cox's regression analysis adjusted for potential confounders demonstrated that the DD and high PS group was associated with MACE when the without DD and low PS group was set as a reference (adjusted HRs 13.69 [95% CI, 1.37–137.32]) (Table 4).

Sensitivity Analysis

A receiver operating characteristic curve analysis was performed such that the ID group was initially analyzed as part of the ND group and then as part of the DD group for predicting MACE. The AUC of the ID and DD group for predicting MACE was 0.676 (95% CI: 0.521–0.830, p value 0.790), while that of the ID and ND group was 0.648 (95% CI: 0.459–0.836, p value 0.096).

Discussion/Conclusion

The present results showed that the prevalence of the DD grade of the new 2016 ASE/EACVI recommendations [11] was 31.7% in hemodialysis patients. On the other hand, a recent study [17] reported that the prevalence of the DD grade was 1.4% in the general popu-

Table 3. Relationships between baseline parameters and hazard ratios for major cardiovascular events (MACE)

Parameter	Univariate analysis		Multivariable analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
ID (vs. ND)	3.83 (0.40–36.83)	0.245	7.55 (0.42–135.95)	0.171*
DD (vs. ND)	10.21 (1.26–83.15)	0.030*	15.99 (1.24–206.05)	0.034**
Age (/y)	1.04 (0.98–1.11)	0.182*	1.02 (0.95–1.11)	0.619
Male	1.28 (0.338–4.810)	0.719		
Dialysis duration (/month)	1.00 (0.99–1.01)	0.432		
Nonsmoker	0.41 (0.11–1.53)	0.184		
Daily alcohol consumption	1.42 (0.51–3.96)	0.508		
Walking independently	0.580 (0.13–2.69)	0.487		
Body mass index (/1 kg/m^2)	0.91 (0.76–1.08)	0.905		
IDWG (/1 kg)	1.21 (0.65–2.25)	0.547		
Predialysis CTR (/1%)	1.064 (0.97–1.17)	0.216		
Kt/V (/1 score)	1.20 (0.28–5.18)	0.812		
Treatment time (≥4 h)	1.50 (0.19–11.72)	0.699		
Predialysis SBP (/10 mm Hg)	1.02 (0.99–1.05)	0.167*	1.01 (0.97–1.05)	0.686
Predialysis DBP (/10 mm Hg)	0.99 (0.95–1.04)	0.528		
Postdialysis SBP (/10 mm Hg)	1.02 (0.99–1.04)	0.205		
Postdialysis DBP (/10 mm Hg)	0.98 (0.91–1.04)	0.447		
Postdialysis OH	1.25 (0.38–4.09)	0.715		
Treatment for hypotension during dialysis	1.57 (0.19–13.14)	0.678		
AVF	2.24 (0.48–10.40)	0.302		
Diabetes	1.36 (0.40–4.64)	0.626		
Previous history of CVD	5.13 (1.36–19.36)	0.016*	2.15 (0.43–10.80)	0.354
Antihypertensive drug use	23.83 (0.01–110,192.17)	0.461		
ESA use	23.83 (0.01–110,192.17)	0.461		
Hemoglobin (/1 g/dL)	0.63 (0.40–1.00)	0.052*	0.84 (0.53–1.35)	0.480
Serum albumin (/1 g/dL)	0.39 (0.10–1.56)	0.184*	1.15 (0.17–7.53)	0.89
Serum aCa (>10.0 mg/dL)	1.03 (0.59–1.83)	0.909		
Serum P (>6 mg/dL)	0.91 (0.57–1.46)	0.682		
CIMT (/mm)	12.68 (2.44–65.86)	0.003*	1.91 (0.26–14.28)	0.528
Plaque score (/1 score)	1.16 (1.06–1.26)	0.001*	1.20 (1.01–1.43)	0.037**
baPWV (/1 cm/s)	1.00 (1.00–1.00)	0.210		
ABI	1.10 (0.03–36.83)	0.958		

Values shown are hazard ratios (95% confidence interval). * *p* value < 0.2; ** *p* value < 0.05. ND, normal diastolic function; ID, indeterminate; DD, diastolic dysfunction; IDWG, interdialytic weight gain; CTR, cardiothoracic ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; OH, orthostatic hypotension; AVF, arteriovenous fistula for vascular access; CVD, cardiovascular disease; ESA, erythropoietin stimulating agents; aCa, adjusted calcium: (4 – serum albumin) + serum calcium if serum albumin < 4.0; P, phosphate; CIMT, carotid intima-media thickness; baPWV, brachial-ankle pulse wave velocity; ABI, ankle brachial index.

lation. The prevalence of DD in dialysis patients was found to be high. Furthermore, postdialysis orthostatic hypotension at least once a week increased proportionally with diastolic function grades. Recent studies including a meta-analysis identified orthostatic hypotension as a risk factor for HF and associated mortality in a general population [18, 19]. Furthermore, in the present prospective cohort study, the DD grade and PS were associated with MACE. This relationship remained largely unchanged even after adjustments for potential confounding factors. When patients were divided into three groups using the median value of PS and the DD grade, patients in the DD and high PS group were associated with MACE when the without DD and low PS group was set as a reference. Furthermore, a sensitivity analysis was performed such that the ID group was initially analyzed as part of the ND group

Table 4. Relationship between the baseline diastolic dysfunction (DD) and/or plaque score (PS) groups and hazard ratios for major cardiovascular events (MACE)

	Diastolic function groups		
	without DD and PS <5.8	with DD or PS ≥5.8	with DD and PS ≥5.8
n	25	25	13
MACE, *n*	1	4	6
Unadjusted model	1.00 (Ref.)	4.26 (0.48–38.14)	15.28 (1.83–127.35)**
Adjusted model[a]	1.00 (Ref.)	2.31 (0.23–23.47)	13.69 (1.37–137.32)**

Values shown are hazard ratios (95% confidence interval). *p* for the interaction = 0.001. ** *p* value <0.05.
[a] Adjusted for age, predialysis systolic blood pressure, previous history of cardiovascular disease, hemoglobin, and serum albumin.

and then as part of the DD group for predicting MACE; however, no significant differences were observed between AUC in these groups.

In the assessment of diastolic function, several parameters and different criteria have been used for evaluations, and a relationship with patient prognosis and several parameters has been verified in a general population [20, 21] as well as in a dialysis population [8–10]. The prevalence and grades of DD have a prognostic impact [22], with a progressively increased risk of mortality being observed with the progression of DD [20], even in patients with a preserved LVEF [21]. In the present study, the DD classification of the four variables for identifying DD by the ASE/EACVI recommendations correlated with MACE. Avramovski et al. [23] identified PS as an independent predictor of cardiovascular mortality in hemodialysis patients. A correlation was noted between PS and LV hypertrophy in hemodialysis patients [24]. The multivariable-adjusted analysis conducted in the present study showed that PS, but not CIMT, ABI, or baPWV, increased proportionally with the LVDD grade, and high PS patients were at a higher risk of MACE. Furthermore, the LVDD grade was found to have a synergic effect with PS. PS may be more sensitive for detecting atherosclerosis than other atherosclerotic factors. All hemodialysis patients already had worse carotid arteries than the general population, and the number of subjects in the present study was small. These factors (i.e., the progression of arteriosclerosis in dialysis patients, compared with the general population, and the small sample size in the study) may have made the arteriosclerotic parameters, other than PS, statistically nonsignificant (= masked).

On the other hand, postdialysis orthostatic hypotension increased proportionally with diastolic function grades. For example, postdialysis orthostatic hypotension occurred at 60% in the DD group versus only 33.3% in the ND group, despite the absence of a significant difference in interdialytic weight gain between these two groups. Therefore, orthostatic hypotension may be associated with LV compliance and LV end-diastolic pressure at the end of hemodialysis, and then with repeated ischemic heart events and MACE.

To the best of our knowledge, this is the first prospective study on hemodialysis patients to have examined the relationship between MACE and LVDD with preserved LV systolic function by the ASE/EACVI recommendations and show a synergic effect with PS. However, the present study has some limitations. It was conducted at a single center, included a relatively small number of patients, and had a short follow-up period, suggesting a selection bias. The prognostic impact of this classification needs to be investigated further in larger studies. Furthermore, we did not evaluate the possible effects of the different medications used to treat hypertension on arterial stiffness and LVDD in the interpretation of our results. In addition, since there is currently no specific gold standard to diagnose LVDD, it was not

possible to establish the diagnostic accuracy of the three different classifications in the general population [17] or hemodialysis patients in the present study. This classification may only have the ability to detect the most advanced cases [17]. Many of our hemodialysis subjects were classified as "indeterminate." Further studies are needed to clarify whether this tendency is specific to hemodialysis patients. Unfortunately, it was not possible to perform comparisons with the classification of DD by other methods in the present study.

In conclusion, patients with hemodialysis had a high incidence of LVDD with preserved LV systolic function by the 2016 ASE/EACVI recommendations and elevated atherosclerosis parameters. The LVDD classification of the ASE/EACVI recommendations was associated with increased MACE and showed a synergic effect with PS for increases in MACE. Therefore, when screening for cardiovascular disease risk factors in hemodialysis patients, particularly in those with postdialysis orthostatic hypotension, we suggest the evaluation of diastolic function by echocardiography, classifications using the ASE/EACVI recommendations, and PS measurements with carotid artery ultrasonography. Further studies on interventions for hemodialysis patients following the specification of DD and PS that will improve outcomes are needed.

Acknowledgement

The authors appreciate the help of the following attending physicians for their participation in the study by collecting data and providing useful suggestions: Akiko Imamura and Miyuki Nishizono.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

All authors have no conflicts of interest to declare.

Funding Sources

The authors have no funding sources to disclose.

Author Contributions

Research idea and study design: R.T. and T.T.; data collection: R.T., R.Y., N.K., S.U., and H.K.; data analysis: T.T.; supervision: S.F.; writing – original draft: R.T. and T.T.; writing – review and editing: H.K., T.I., Y.S., K.K., and S.F.

References

1 Redfield MM, Jacobsen SJ, Burnett JC Jr, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure. JAMA. 2003 Jan;289(2):194-202.
2 Genovesi S, Valsecchi MG, Rossi E, Pogliani D, Acquistapace I, De Cristofaro V, et al. Sudden death and associated factors in a historical cohort of chronic haemodialysis patients. Nephrol Dial Transplant. 2009 Aug;24(8):2529–36.

3 Harnett JD, Foley RN, Kent GM, Barre PE, Murray D, Parfrey PS. Congestive heart failure in dialysis patients: prevalence, incidence, prognosis and risk factors. Kidney Int. 1995 Mar;47(3):884–90.
4 Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med. 2006 Jul;355(3):251–9.
5 Halley CM, Houghtaling PL, Khalil MK, Thomas JD, Jaber WA. Mortality rate in patients with diastolic dysfunction and normal systolic function. Arch Intern Med. 2011 Jun;171(12):1082–7.
6 Wan SH, Vogel MW, Chen HH. Pre-clinical diastolic dysfunction. J Am Coll Cardiol. 2014 Feb;63(5):407–16.
7 Antlanger M, Aschauer S, Kopecky C, Hecking M, Kovarik JJ, Werzowa J, et al. Heart failure with preserved and reduced ejection fraction in hemodialysis patients: prevalence, disease prediction and prognosis. Kidney Blood Press Res. 2017;42(1):165–76.
8 Sharma R, Pellerin D, Gaze DC, Mehta RL, Gregson H, Streather CP, et al. Mitral peak Doppler E-wave to peak mitral annulus velocity ratio is an accurate estimate of left ventricular filling pressure and predicts mortality in end-stage renal disease. J Am Soc Echocardiogr. 2006 Mar;19(3):266–73.
9 Tripepi G, Benedetto FA, Mallamaci F, Tripepi R, Malatino L, Zoccali C. Left atrial volume monitoring and cardiovascular risk in patients with end-stage renal disease: a prospective cohort study. J Am Soc Nephrol. 2007 Apr;18(4):1316–22.
10 Han JH, Han JS, Kim EJ, Doh FM, Koo HM, Kim CH, et al. Diastolic dysfunction is an independent predictor of cardiovascular events in incident dialysis patients with preserved systolic function. PLoS One. 2015 Mar;10(3):e0118694.
11 Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2016 Apr;29(4):277–314.
12 Chow B, Rabkin SW. The relationship between arterial stiffness and heart failure with preserved ejection fraction: a systemic meta-analysis. Heart Fail Rev. 2015 May;20(3):291–303.
13 Harada M, Tabako S. Carotid atherosclerosis is associated with left ventricular diastolic function. J Echocardiogr. 2016 Sep;14(3):120–9.
14 Albu A, Fodor D, Bondor C, Poantă L. Arterial stiffness, carotid atherosclerosis and left ventricular diastolic dysfunction in postmenopausal women. Eur J Intern Med. 2013 Apr;24(3):250–4.
15 Asakawa T, Hayashi T, Tanaka Y, Joki N, Hase H. Changes over the last decade in carotid atherosclerosis in patients with end-stage kidney disease. Atherosclerosis. 2015 Jun;240(2):535–43.
16 Otterstad JE, Froeland G, St John Sutton M, Holme I. Accuracy and reproducibility of biplane two-dimensional echocardiographic measurements of left ventricular dimensions and function. Eur Heart J. 1997 Mar;18(3):507–13.
17 Almeida JG, Fontes-Carvalho R, Sampaio F, Ribeiro J, Bettencourt P, Flachskampf FA, et al. Impact of the 2016 ASE/EACVI recommendations on the prevalence of diastolic dysfunction in the general population. Eur Heart J Cardiovasc Imaging. 2018 Apr;19(4):380–6.
18 Xin W, Lin Z, Li X. Orthostatic hypotension and the risk of congestive heart failure: a meta-analysis of prospective cohort studies. PLoS One. 2013 May;8(5):e63169.
19 Xin W, Lin Z, Mi S. Orthostatic hypotension and mortality risk: a meta-analysis of cohort studies. Heart. 2014 Mar;100(5):406–13.
20 Little WC, Oh JK. Echocardiographic evaluation of diastolic function can be used to guide clinical care. Circulation. 2009 Sep;120(9):802–9.
21 Aljaroudi W, Alraies MC, Halley C, Rodriguez L, Grimm RA, Thomas JD, et al. Impact of progression of diastolic dysfunction on mortality in patients with normal ejection fraction. Circulation. 2012 Feb;125(6):782–8.
22 Kuznetsova T, Thijs L, Knez J, Herbots L, Zhang Z, Staessen JA. Prognostic value of left ventricular diastolic dysfunction in a general population. J Am Heart Assoc. 2014 Apr;3(3):e000789.
23 Avramovski P, Avramovska M, Sikole A. B-flow imaging estimation of carotid and femoral atherosclerotic plaques: vessel walls rheological damage or strong predictor of cardiovascular mortality in chronic dialysis patients. Int Urol Nephrol. 2016 Oct;48(10):1713–20.
24 Mowlaie M, Nasri H. Close association of arterial plaques with left ventricular hypertrophy and ejection fraction in hemodialysis patients. J Nephropharmacol. 2014 Jan;3(1):9–12.