Retrospective Clinical Research Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
49(3) 1–10

DOI: 10.1177/0300060521997588
journals.sagepub.com/home/imr

SAGE

Differences between diabetic and non-diabetic nephropathy patients in cardiac structure and function at the beginning of hemodialysis and their impact on the prediction of mortality

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Abstract

Objectives: To characterize differences in cardiac structure and function in hemodialysis (HD) patients with diabetic nephropathy (DN) and in those without using echocardiography and to determine their impact on the prediction of mortality using echocardiographic parameters.

Methods: Clinical, laboratory, and echocardiographic data were collected from patients commencing HD.

Results: Compared with those without DN, patients with DN had lower peak velocity of the early diastolic wave (e′), larger left atria, and higher peak early diastolic velocity (E)/e′ and peak velocity of tricuspid regurgitation (TR). In addition, a larger proportion of DN patients had a combination of left ventricular (LV) diastolic dysfunction, cardiac valve calcification, moderate-to-severe cardiac valve regurgitation (CVR), and at least moderate pericardial effusion (PE). After accounting for age, sex, smoking, hypertension, hemoglobin, and albumin, DN was responsible for e′ $<$ 10 cm/s, E/e′ $>$13 m/s, TR $>$2.8 m/s, LV diastolic dysfunction, CVR, and PE. LV diastolic dysfunction and E/e′ $>$13 were the most useful predictors of mortality in patients with DN.

Conclusions: Patients with DN who undergo HD tend to have worse LV diastolic function and are more likely to have heart valve problems. LV diastolic dysfunction and E/e′ are predictors of death in DN patients.

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Keywords
Diabetic nephropathy, echocardiography, hemodialysis, mortality, subgroup analysis, left ventricular diastolic dysfunction, peak early diastolic velocity

Date received: 11 January 2021; accepted: 21 January 2021

Introduction

Diabetic nephropathy (DN) is a main cause of chronic renal failure in both China and western countries.[1,2] According to the United States Renal Data Survey, DN is a major contributor to the increasing incidence of end-stage renal disease (ESRD).[3] In addition, the incidence of DN has been shown to be gradually increasing in Chinese ESRD patients.[4] People with DN are at high risk of developing cardiovascular complications, which are the leading cause of death in diabetic patients undergoing hemodialysis.[5,6] We hypothesized that changes in cardiac structure and function may be responsible for this greater mortality. Because of its relative accessibility and simplicity, echocardiography is commonly used for the clinical evaluation of cardiac structure and function. Therefore, in the present study, we aimed to determine whether cardiac structure and function, assessed echocardiographically, are significantly worse in dialysis-dependent ESRD patients with DN than in those without DN, and the effect on mortality.

Materials and methods

Participants and clinical and laboratory data collection

We studied patients who started regular HD at the Second Affiliated Hospital of Soochow University between 1 January 2010 and 31 August 31 2016. They were all over 18 years of age and commenced scheduled dialysis three times a week *via* an arteriovenous fistula. The exclusion criteria were acute kidney injury, acute exacerbation of chronic kidney disease, incomplete medical records, and valvular or other structural heart disease.

Clinical and laboratory data were collected from the electronic medical records of the Second Affiliated Hospital of Soochow University at the time when each participant reached a stable target weight. The clinical data recorded were the etiological diagnosis of their chronic kidney disease; age; sex; body mass index (BMI); history of smoking, hypertension, coronary artery disease (CAD); and their medication. DN was diagnosed by a nephrologist using clinical criteria (the presence of diabetes, diabetic retinopathy, and proteinuria) or was diagnosed pathologically, on the basis of the presence of Kimmelstiel–Wilson nodules. A systolic blood pressure >130 mmHg or a diastolic blood pressure >80 mmHg was regarded as hypertension. Coronary stenosis >50%, identified using coronary angiography or computed tomography angiography led to a diagnosis of CAD. The laboratory data recorded were venous glucose (Glu); hemoglobin (Hb); and the serum albumin (Alb), C-reactive protein (CRP), creatinine (Scr), calcium (Ca), phosphorus (P), and parathyroid hormone releasing hormone (PTH) concentrations. Residual kidney function (RKF) was estimated from the residual urine volume in HD patients.

This study was approved by the Ethics Committee of The Second Affiliated

Hospital of Soochow University and is registered in the Chinese Clinical Trial Registry (ChiCTR1900024999). The study protocol was consistent with the principles of the Declaration of Helsinki. Verbal informed consent was obtained from all the participants.

Echocardiography

To mitigate the effects of volume overload, echocardiographic data were collected on dialysis days after the HD had been completed. We recorded the left atrial diameter (LAD), left ventricular (LV) internal diameter at the end of diastole (LVIDD), interventricular septal thickness (IVST), and left ventricular posterior wall thickness (LVPWT). The LAD index (LADI = LAD/body surface area [BSA]) and the LVIDD index (LVIDDI = LVIDD/BSA) were also calculated. We used chamber diameter and wall thickness (LVPWT and IVST) to calculate LV mass, according to the equation: LV mass (g) $= 0.8 \times 1.04 \times [(\text{LVIDD} + \text{LVPWT} + \text{IVST})^3 - \text{LVIDD}^3] + 0.6$.[7] The LV mass index (LVMI) was calculated as LV mass/height$^{2.7}$, as suggested by the 2013 European Society of Cardiology/European Society of Hypertension guidelines.[8] The left ventricular ejection fraction (LVEF) was calculated using the modified Simpson method from the apical four- and two-chamber views. Cardiac valve calcification (CVC) was diagnosed in the presence of bright echoes of >1 mm on one or more cusps of the aortic valve, mitral valve, or mitral annulus.[9] The presence of valvular stenosis (CVS) and moderate-to-severe cardiac valve regurgitation (CVR) were also recorded. The peak early diastolic velocity (E) of the mitral orifice was measured using pulsed Doppler on the apical four-chamber view. The peak velocity of the early diastolic wave (e′) was measured using pulsed-wave tissue Doppler, with the sample volume being placed close to the mitral valve annulus in the lateral wall on the apical four-chamber view. E/e′ was also calculated. The peak velocity of tricuspid regurgitation (TR) was measured on the apical four-chamber view using continuous-wave Doppler. LV diastolic dysfunction was assessed according to the guidelines of the American Society of Echocardiography.[12] We also recorded if the right atrium (RA) or right ventricle (RV) were enlarged. The presence of moderate-to-severe pericardial effusion (PE) was also recorded. Echocardiographic measurements were performed by experienced echocardiography technicians.

Statistical analysis

Statistical analysis was performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA) and R statistical package version 3.6.1 (www.r-project.org). Normally distributed continuous data are presented as mean $\pm$ SD and were compared using Student's *t*-test. Non-normally distributed continuous data are presented as median with interquartile range and were compared using the Mann–Whitney U-test. Categorical data are presented as the number of cases and percentages and were compared using the chi-square test. Multivariate logistic regression modeling was used to evaluate the effect of DN on the heart. Subgroup analysis of a multivariate Cox proportional regression model was used to evaluate the difference in the predictive value of echocardiographic indicators for mortality in participants with and without DN. A two-tailed P value < 0.05 was considered to represent statistical significance.

Results

Baseline clinical and laboratory characteristics of the sample

One hundred and seventy-four patients were enrolled in the study. Table 1

Table 1. Clinical characteristics of the study groups.

	Entire sample (n = 174)	DN group (n = 48)	Non-DN group (n = 126)	*P*-value
Age, years	56 ± 17	62 ± 14	54 ± 18	0.001
Male sex, n (%)	121 (69.5)	34 (70.8)	87 (69.0)	0.819
Smoking, n (%)	29 (16.7)	8 (16.7)	21 (16.7)	1
BMI, kg/m^2	20.8 (19.6, 22.6)	21.3 (19.8, 23.3)	20.8 (19.6, 22.6)	0.379
Hypertension, n (%)	134 (77.0)	41 (85.4)	93 (73.8)	0.104
CAD, n (%)	7 (4.0)	6 (12.5)	1 (0.8)	0.002
Glu, mmol/L	4.84 (4.46, 5.61)	5.67 (4.62, 7.56)	4.74 (4.46, 5.18)	<0.001
Hb, g/L	86.0 ± 20.2	85.4 ± 15.8	86.3 ± 21.7	0.76
Alb, g/L	32.94 ± 6.35	32.27 ± 6.37	33.20 ± 6.35	0.391
CRP, mg/L	7.0 (6.3, 16.8)	7.2 (6.5, 21.1)	7.0 (6.3, 16.8)	0.119
Scr, μmol/L	764 (513, 1090)	520 (383, 739)	861 (580, 1180)	<0.001
24-hour urine output, mL	570.6 ± 449.0	643.9 ± 457.6	535.0 ± 440.8	0.004
P, mmol/L	1.62 (1.28, 2.14)	1.41 (1.15, 1.88)	1.72 (1.34, 2.21)	0.005
Ca, mmol/L	2.04 ± 0.26	2.04 ± 0.23	2.03 ± 0.27	0.784
Ca×P, mg^2/dL^2	39.8 (31.3, 53.4)	35.5 (28.5, 46.2)	41.2 (34.3, 54.8)	0.008
PTH, pg/mL	215.2 (110.6, 390.1)	150.1 (75.3, 283.4)	247.7 (131.4, 439.0)	0.002
ACEi or ARB, n (%)	67 (38.5)	23 (47.9)	44 (34.9)	0.115
CCB, n (%)	123 (70.7)	37 (77.1)	86 (68.3)	0.253
α-blocker, n (%)	62 (35.6)	21 (43.8)	41 (32.5)	0.168
β-blocker, n (%)	85 (48.9)	25 (52.1)	60 (47.6)	0.599
Loop diuretic, n (%)	74 (42.5)	24 (50.0)	50 (39.7)	0.219

Data are mean ± SD (compared using Student's *t*-test), median with interquartile range (compared using the Mann–Whitney U-test), or number of cases and percentage (compared using the chi-square test).
DN, diabetic nephropathy; BMI, body mass index; CAD, coronary artery disease; Glu, glucose; Hb, hemoglobin; Alb, albumin; CRP, C-reactive protein; Scr, serum creatinine; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CRP, C-reactive protein; PTH, parathyroid hormone.

shows the baseline clinical characteristics of the sample. Their mean age was 56 ± 17 years and 69.5% were men (121/174). Of the participants, 48 had DN and 126 did not. Of the non-DN participants, most had glomerulonephropathy (73/126). Compared with the non-DN group, the DN group were older ($p = 0.001$) and had a higher prevalence of CAD ($p = 0.002$), Glu ($p < 0.001$), and urine output ($p = 0.004$); and lower Scr ($p < 0.001$), P ($p = 0.005$), Ca×P ($p = 0.008$), and PTH ($p = 0.002$) concentrations. Forty-three of the participants had died by the end of the 3-year study period, of whom 21 had DN and 22 did not.

Differences in echocardiographic parameters between the DN and non-DN groups

Table 2 shows that the DN group had a larger LAD ($p = 0.022$) and LADI ($p = 0.041$), and more heart valve problems, including CVC ($p = 0.016$) and CVR ($p = 0.007$). The participants with DN also had a lower e′ ($p < 0.001$), but higher TR

Table 2. Comparisons of echocardiographic parameters in the DN and non-DN groups.

	DN group (n = 48)	non-DN group (n = 126)	*P*-value
LVEF (%)	60.2 (54.1, 67.3)	62.7 (56.6, 67.5)	0.402
LAD (mm)	44.65 ± 7.46	41.80 ± 7.21	0.022
LADI (mm/m^2)	27.79 ± 5.21	26.09 ± 4.72	0.041
LVIDD (mm)	52.4 (49.1, 55.8)	52.3 (48.0, 56.8)	0.799
LVIDDI (mm/m^2)	32.98 ± 5.16	32.65 ± 3.79	0.693
IVST (mm)	11.9 (10.0, 13.0)	10.7 (9.9, 12.6)	0.366
LVPWT (mm)	11.0 (9.8, 13.0)	10.1 (9.6, 12.0)	0.292
LV mass (g)	220.8 (188.8, 317.1)	220.2 (167.9, 280.9)	0.293
LVMI (g/m$^{2.7}$)	55.0 (49.3, 79.9)	56.6 (44.1, 67.4)	0.304
e′ (cm/s)	7.7 (6.0, 9.0)	9.0 (8.0, 12.0)	<0.001
E/e′	12.44 (9.48, 15.50)	8.56 (6.82, 11.96)	<0.001
TR (m/s)	2.61 (2.29, 3.20)	2.40 (2.14, 2.71)	0.007
LV diastolic dysfunction, n (%)	25 (52.1%)	23 (18.3%)	<0.001
RA dilatation, n (%)	10 (20.8%)	19 (15.1%)	0.363
RV dilatation, n (%)	8 (16.7%)	10 (7.9%)	0.158
CVC, n (%)	18 (37.5%)	25 (19.8%)	0.016
CVS, n (%)	2 (4.2%)	5 (4.0%)	0.953
CVR, n (%)	15 (31.3%)	17 (13.5%)	0.007
PE, n (%)	28 (58.3%)	49 (38.9%)	0.026

Data are mean ± SD (compared using Student's *t*-test), median with interquartile range (compared using the Mann–Whitney U-test), or number of cases and percentage (compared using the chi-square test).
DN, diabetic nephropathy; non-DN, no DN; LVEF, left ventricular ejection fraction; LAD, left atrial diameter; LADI, LAD index; LVIDD, left ventricular internal diameter at the end of diastole; LVIDDI, LVIDD index; IVST, intraventricular septal thickness; LVPWT, left ventricular posterior wall thickness; LV mass, left ventricular mass; LVMI, LV mass index; e′, peak velocity of early diastolic wave; E/e′, peak early diastolic velocity/e′; TR, peak velocity of tricuspid regurgitation; LV, left ventricular; RA, right atrial; RV, right ventricular; CVC, cardiac valve calcification; CVS, cardiac valvular stenosis; CVR, cardiac valve regurgitation; PE, pericardial effusion.

($p = 0.007$) and E/e′ ($p < 0.001$). In addition, the DN group had a higher prevalence of LV diastolic dysfunction ($p < 0.001$).

Identification of echocardiographic parameters that are associated with DN using multivariate logistic regression

Echocardiographic parameters were dichotomized according to guideline criteria (Figure 1), and after adjustment for age, sex, smoking, hypertension, Hb, and Alb using a multivariate logistic regression model, DN was shown to have an effect on e′ <10 cm/s (hazard ratio [HR]: 2.968, 95% confidence interval [CI]: 1.28–6.89), E/e′ >13 (HR: 2.76, 95% CI: 1.27–6.01), TR >2.8 m/s (HR: 2.56, 95% CI: 1.06–6.17), LV diastolic dysfunction (HR: 3.66, 95% CI: 1.67–8.05), CVR (HR: 2.97, 95% CI: 1.25–7.08), and PE (HR: 2.25, 95% CI: 1.08–4.68) (Table 3).

Subgroup analysis of the predictive value of echocardiographic parameters for mortality in DN and non-DN participants

The predictive value of echocardiographic parameters for mortality in each group was analyzed using a multivariate Cox proportional regression model. After adjustment for age, sex, and hypertension, LAD (HR: 1.55, 95% CI: 1.08–2.22, per 5 mm), LADI (HR: 2.015, 95% CI: 1.23–3.26, per

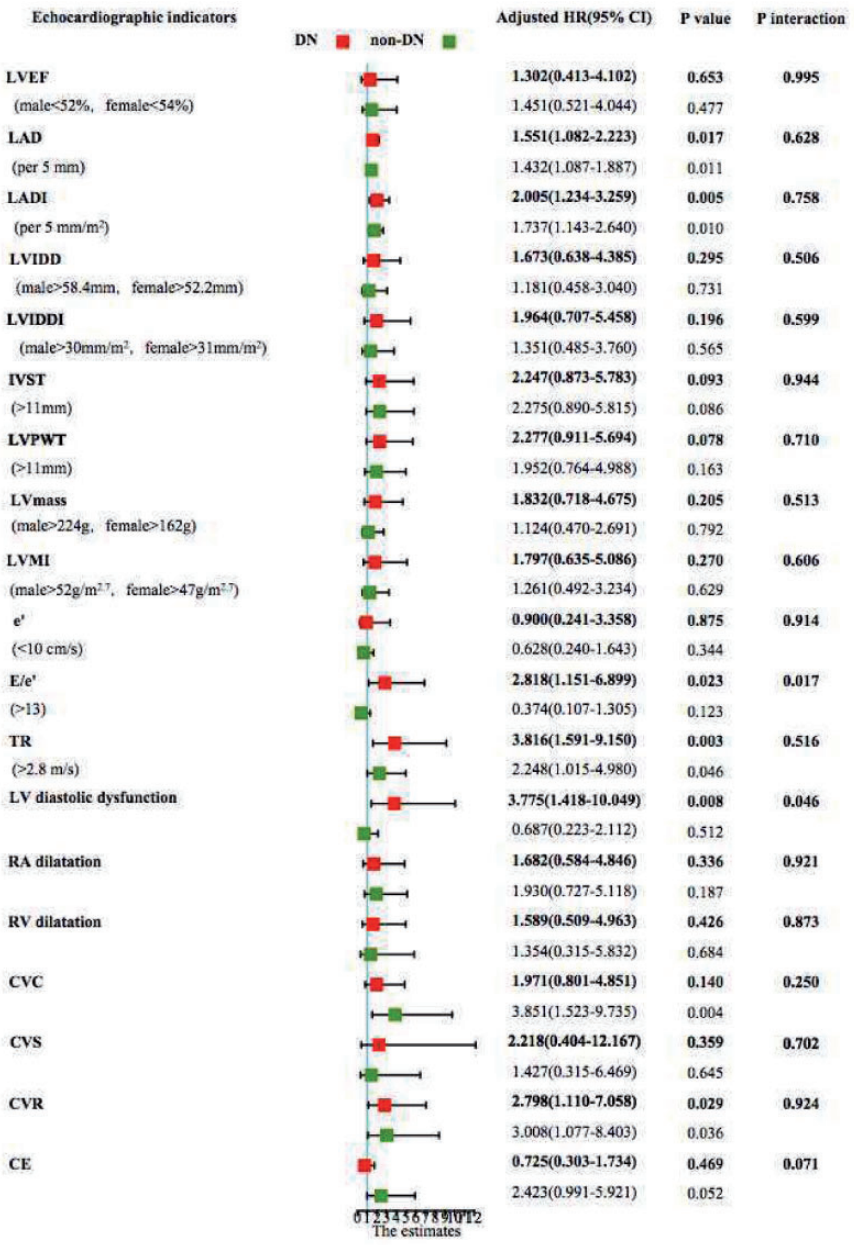

Figure 1. Stratified analysis of the predictive value of echocardiographic parameters for the mortality of participants with or without diabetic nephropathy, performed using a multivariate sub-distribution hazard model, after adjustment for age, sex, and hypertension.

DN, diabetic nephropathy; non-DN, no DN; HR, hazard ratio; CI, confidence interval; LVEF, left ventricular ejection fraction; LAD, left atrial diameter; LADI, LAD index; LVIDD, left ventricular internal diameter at the end of diastole; LVIDDI, LVIDD index; IVST, intraventricular septal thickness; LVPWT, left ventricular posterior wall thickness; LV mass, left ventricular mass; LVMI, LV mass index; e′, peak velocity of early diastolic wave; E/e′, peak early diastolic velocity/e′; TR, peak velocity of tricuspid regurgitation; LV, left ventricular; RA, right atrial; RV, right ventricular; CVC, cardiac valve calcification; CVS, cardiac valvular stenosis; CVR, cardiac valve regurgitation; PE, pericardial effusion.

Table 3. Echocardiographic parameters associated with DN after adjustment for age, sex, smoking, hypertension, Hb, and Alb.

	P-value	HR	95% CI
e′ <10 cm/s	0.011	2.968	(1.279–6.890)
E/e′ >13	0.010	2.762	(1.269–6.013)
TR >2.8 m/s	0.036	2.562	(1.064–6.167)
LV diastolic dysfunction	0.001	3.662	(1.665–8.053)
CVR	0.014	2.973	(1.249–7.076)
PE	0.030	2.250	(1.082–4.679)

DN, diabetic nephropathy; Hb, hemoglobin; Alb, albumin; HR, hazard ratio; CI, confidence interval; e′, peak velocity of early diastolic wave; E/e′, peak early diastolic velocity/e′; TR, peak velocity of tricuspid regurgitation; LV, left ventricular; CVR, cardiac valve regurgitation; PE, pericardial effusion.

5 mm/m^2), E/e′ >13 (HR: 2.82, 95% CI: 1.15–6.90), TR >2.8 m/s (HR: 3.82, 95% CI: 1.59–9.15), LV diastolic dysfunction (HR: 3.78, 95% CI: 1.42–10.05), and CVR (HR: 2.80, 95% CI: 1.11–7.06) were predictors of mortality in the DN group; and LAD (HR: 1.43, 95% CI: 1.09–1.89, per 5 mm), LADI (HR: 1.74, 95% CI: 1.14–2.64, per 5 mm/m^2), TR >2.8 m/s (HR: 2.25, 95% CI: 1.02–4.98), CVC (HR: 3.85, 95% CI: 1.52–9.74), and CVR (HR: 3.01, 95% CI: 1.08–8.40) were predictors of mortality in the non-DN group. The parameters that had *P*-values indicating an interaction of < 0.05 were E/e′>13 (p interaction $= 0.017$) and LV diastolic dysfunction (p interaction $= 0.046$) (Figure 1).

Discussion

The pathogenesis, pathological changes, clinical manifestations, complications, treatment, and prognosis of patients with and without DN significantly differ.[10] Patients with DN show a high incidence of cardiovascular disease because of abnormal glucose metabolism, insulin resistance, vascular endothelial damage, and toxin accumulation in the body.[11] Many previous studies have evaluated the cardiac structure and function of patients with diabetes or chronic kidney disease, but few have assessed these parameters in patients with DN that are already on dialysis. In the present study we compared the echocardiographic parameters of patients with and without DN at the beginning of HD, and found significant differences in cardiac structure and function between the two groups. In addition, we found that the various echocardiographic parameters were of different utility for the prediction of mortality in the two patient groups.

In the present study, we found that the participants with DN were older and had a higher prevalence of CAD than the non-DN participants. In addition, the participants with DN had a lower Scr and higher residual urine volume, which may be because patients with DN tend to start dialysis earlier in life. In addition, and similar to the results obtained by Chen[12] and Wahl[13], the patients with DN in the present study had lower P, Ca×P, and PTH, which may be because high circulating glucose concentrations affect PTH secretion[14] and residual renal function.

On echocardiography, the participants with DN had larger left atria, higher E/e′ and TR, and lower e′. These four parameters are closely related to LV diastolic function, according to the American Society of Echocardiography.[15] We also found that DN patients had more heart valve problems, including CVC and CVR. Furthermore, the prevalence of PE in

participants with DN was higher than in those without. After accounting for the effects of age, sex, smoking, hypertension, Hb, and Alb, DN was associated with poorer LV diastolic function, and higher prevalences of CVR and PE.

Valvular heart disease, including CVC, CVR, and CVS, is common in patients with chronic kidney disease.[16] Previous studies have found that the incidence of CVC is higher in patients with ESRD and that this may be related to age, the duration of dialysis, diabetes, calcium-phosphate metabolism, inflammation, and malnutrition.[17,18] The participants with DN in the present study had a higher prevalence of CVC, which is consistent with previous findings.[19,20] Their older age and poorer lipid profile may explain this. Irrespective of the presence of CVC, cardiac enlargement and functional regurgitation may predispose to CVR. Although mitral and tricuspid valve regurgitation often do not markedly affect function and are potentially reversible in CKD patients, moderate and severe CVR, which were recorded in the present participants, could eventually result in changes in cardiac structure and function and increase mortality.

LV systolic dysfunction is common in ESRD patients. Previous studies have suggested that in addition to old age, hypertension, diabetes, and LV hypertrophy, this can be related to anemia, a microinflammatory response, and disorders in bone mineral metabolism.[21,22] Through a variety of mechanisms, cardiac damage (including LV diastolic dysfunction) occurs earlier in patients with DN,[23] and it has been shown that LV diastolic dysfunction is associated with higher rates of morbidity and mortality.[24] An important study by Sharma *et al*.[25] showed that E/e′, a key echocardiographic parameter, is the most reliable indicator of LV diastolic dysfunction in HD patients, and in the present study, we have shown that E/e′ may also be more sensitive predictor of mortality in patients with DN who are undergoing HD than other parameters. A study by Han *et al*. evaluated the predictive value of echocardiographic parameters for clinical events in patients who are starting HD, and found that E/e′ was an independent predictor of mortality and heart failure in dialysis patients.[26]

The present study had several limitations. First, it was a single-center study, and therefore the conclusions may not be generalizable to other populations. Second, the sample size of the study was small, which reduces the reliability of the conclusions. Finally, we did not evaluate some relevant echocardiographic parameters, such as pulmonary arterial pressure and right heart function.

In conclusion, we have shown that patients with DN who are on HD tend to have worse LV diastolic function and more frequent heart valve problems. In addition, poor LV diastolic function, and especially E/e′, may represent a good predictor of mortality in patients with DN.

Acknowledgments

This study was supported by the Department of Cardiology and Nephrology of the Second Affiliated Hospital of Soochow University. We thank all the staff for their assistance.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This work was supported by the Science and Technology Development Plan of Suzhou City, China (Grant No: SYS2019061, to Xiaosong Gu) and the MSD Cholesterol Fund of China Heart House of the China Cardiovascular Association (Grant NO. 2017-CCA-Msdlipid-014).

Author contributions

All the authors contributed to study design, data analysis, and article writing and revision, and agree to take responsibility for the results.

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