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REVIEW ARTICLE

The role of echocardiographic study in patients with chronic kidney disease

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Despite the recent enormous advances in medicine, high mortality and morbidity rates among the chronic kidney disease (CKD) patients remain an important but unresolved issue. Cardiovascular disease is a major cause of mortality and morbidity in patients with CKD. Abnormal left ventricular geometry and functions are common in this patient group and have been proven to be correlated with a high cardiovascular mortality/morbidity and all-cause mortality. For this reason, echocardiographic study plays an important role in evaluating cardiac structure and functions as well as in stratifying prognostic risk. We here summarize the reported findings on the usefulness of echocardiographic methodologies and identify their roles in diagnostic and prognostic clinical approaches.

Introduction

Cardiovascular disease (CVD) is a major cause of mortality and morbidity in patients with chronic kidney disease (CKD).[1–4] Renal function impairment, indicated by reduced estimated glomerular filtration rate (eGFR), is a powerful prognostic predictor of mortality, cardiovascular events, and hospitalization.[5,6] In addition, despite advances in dialysis therapy and patient care, end-stage renal disease

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(ESRD) is still notorious for high mortality.[4,7] There are several possible explanations for poor prognosis of CKD patients, including traditional cardiovascular risk factors (i.e., hypertension, diabetes mellitus, and dyslipidemia), nontraditional factors (e.g., malnutrition, inflammation, and oxidative stress), and CKD-related risk factors (e.g., atherosclerosis, anemia, altered calcium–phosphate metabolism).[8–15] These factors may contribute to the development and deterioration of the coronary artery disease (CAD), microvasculopathy, valvulopathy, cardiomyopathy, and arrhythmias.[9,16–22]

Cardiac abnormalities, especially abnormal left ventricular (LV) geometry and functions, are frequently detected in CKD patients and have been proven to be correlated with high cardiovascular mortality/morbidity and all-cause mortality.[2,3,23–25] Early identification of such high-risk patients should thus allow physicians to optimize the therapeutic interventions, which may lower morbidity and mortality.[7]

Role of echocardiography

Nowadays, cardiac magnetic resonance imaging (cMRI) is the widely accepted reference standard of noninvasive imaging modalities to evaluate cardiac morphology (e.g., LV volume and mass) and function [e.g., ejection fraction (EF) and cardiac output].[26] However, there are several major limitations of cMRI in daily practice, such as its high costs, nonportability, and having little or no prognostic evidence of several CVDs.[27] These factors limit its clinical application. In addition, although the risk of gadolinium toxicity in advanced CKD patients is rare, the serious complication of nephrogenic systemic fibrosis is still the major concern.[28,29]

Echocardiography is another option to evaluate cardiac geometry and functions. Although echocardiography is operator dependent, over the past several years the accuracy of echocardiographic measurements had been proven to be closely correlated with histologic findings and had also been well validated in epidemiologic studies. Therefore, echocardiographic study may play a critical role in evaluating cardiac functions, stratifying prognostic risk factors, and assessing the effect of therapeutic interventions.

Traditionally, two-dimensional echocardiography (2DE) and M-mode imaging have been viewed as capable of assessing LV geometry and quantifying LV mass, end-diastolic and end-systolic volumes, and systolic function.[30] Furthermore, the Doppler modality can provide indirect information about LV relaxation, which indicates the LV diastolic function.[31]

LV hypertrophy

LV hypertrophy is one of the most common cardiac geometric abnormalities in CKD patients.[32–34] It is also acknowledged as an independent prognostic predictor, especially among dialysis patients.[34–36] Therefore, LV hypertrophy is regarded as a treated target.

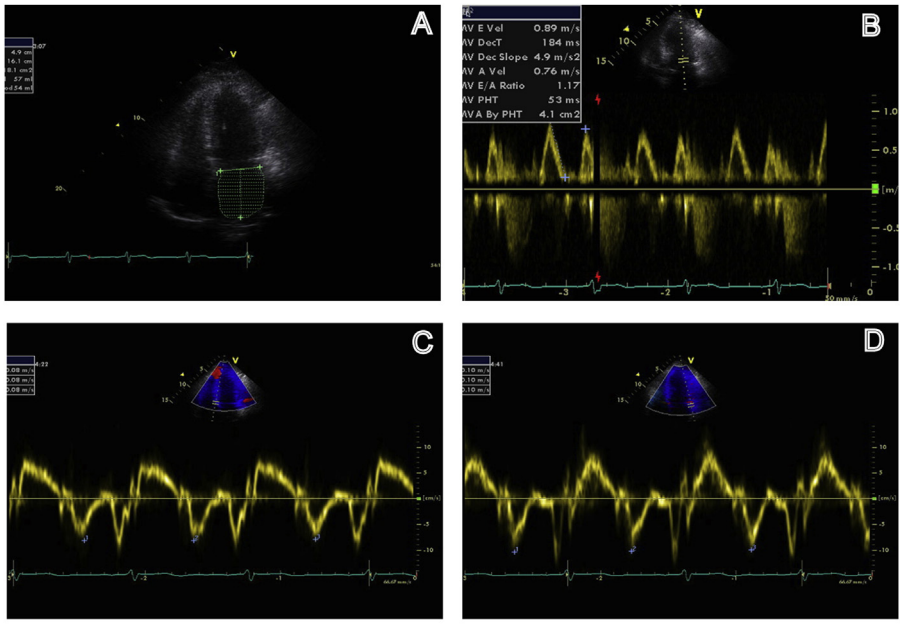
The finding of an increase in LV hypertrophy with simultaneous decrease in renal function indicates the inverse association between the LV mass and the stage of renal failure.[23,32,37] LV hypertrophy is reported in 16–50% of early and intermediate CKD (Stages 1–3) patients, 50–70% of advanced CKD (Stages 4 and 5) patients, and in up to 70–90% of regular dialysis patients.[22,25,32,33,37] Such variation between different reports may result from the different cutoff values of LV hypertrophy.[32,33,38] Notwithstanding this variation, the prognostic power of LV hypertrophy in CKD patients is well recognized.

Given that LV mass is recognized to be proportional to body size, it should be indexed by body surface for clinical studies and daily practice. According to the recommendations of the American Society of Echocardiography (ASE) and the European Association of Echocardiography (EAE), the cutoff value of LV hypertrophy is > 115 gm/m^2 for men and >95 gm/m^2 for women.[30] However, hemodialysis patients may be subject to large body-weight variations, which may lead to evaluation errors by body surface indexation.[32,39] Thus, some experts recommended indexing LV mass by height to the 2.7 power to assess LV mass accurately in hemodialysis patients.[40] Nevertheless, there has not been to date any head-to-head comparison study to address the fundamental question of whether indexation by height can more accurately evaluate LV mass than indexation by body surface in hemodialysis patients. Therefore, standardization of LV mass formulas by echocardiography guidelines should be helpful to prevent variations between clinical studies and patient cares.

LV diastolic function

Renal impairment and cardiac dysfunction frequently coexist. Several mechanisms account for CKD-related cardiomyopathy, including CAD, microvasculopathy, reduction of coronary reserve, and alternations of LV geometry in response to the overload of pressure and volume. To maintain an adequate cardiac output, ventricular remodeling occurs in response to such alternations. However, such ventricular remodeling is pathologic and will lead to chamber dilatation, LV hypertrophy, and LV systolic as well as diastolic dysfunction. LV diastolic dysfunction is common in CKD patients,[22,32,33,41] with causes being multifactorial. There is evidence that impairment of LV diastolic relaxation develops along with the activation of circulating plasminogen activator inhibitor-1.[42] Myocardial fibrosis is also a major determinant of diastolic function.[43–46] The plasma level of carboxy-terminal peptide of procollagen type I has thus been suggested as a useful marker for determining the level of fibrotic activity[44–46] and diastolic dysfunction.[47,48]

Diastolic function is related to myocardial relaxation and LV compliance/stiffness. The former is determined by load, myocardial inactivation, and asynchrony,[49] whereas the latter describes the relationship between LV diastolic pressure and volume, and is determined by the cardiomyocytes and the interstitial matrix. Based on the ASE/EAE guidelines,[31] comprehensive LV diastolic function should be evaluated with several modalities, such as 2DE, which can quantify LV mass, left atrial (LA) volume (Figure 1A), and LA function. It is also noteworthy that the measurement of LA volume is highly reliable and clinically important to assess LV diastolic function. Moreover, LA



E

Parameters	Values
E	89 cm/s
e' (septal)	8 cm/s
e' (lateral)	10 cm/s
e' (average)	9 cm/s
Average E/e'	9.89

Figure 1 An example of images captured from an end-stage renal disease patient (49-year-old male) with low E/e′ ratio. (A) End-systolic left atrial (LA) volume with a volume index of 28.6 mL/m^2 was acquired in the apical four-chamber view. LA volume = 54 mL; body surface area = 1.89 m^2. (B) Pulsed-wave Doppler, and (C, D) tissue Doppler were performed in the apical four-chamber view to acquire mitral inflow early diastolic velocity (parameter E), septal, and lateral tissue Doppler signals (e′) of the mitral annulus. Average septal e′ = 8 cm/s; average lateral e′ = 10 cm/s. (E) Echocardiography parameters: the average (septal and lateral) e′ velocity was used to calculate the E/e′ ratio.

volume index is an independent prognostic predictor in CKD patients.[50,51] However, as dilated LA is not uncommon in patients without diastolic dysfunction, such as anemia and bradycardia, it is important to interpret LA volume with patients' clinical condition, other chambers' volumes, and Doppler parameters of LV relaxation.

To assess LV diastolic function, pulsed-wave (PW) Doppler, which is performed in the apical four-chamber view to acquire mitral inflow velocities, is used to evaluate LV filling parameters (Figure 1B). The primary transmitral PW Doppler measurements include peak E (early diastole) and peak A (late diastole) velocities, the E/A ratio, the deceleration time of the early filling velocity, and the isovolumic relaxation time. The mitral inflow patterns include normal, impaired LV relaxation (E/A $<$ 1, grade 1 diastolic dysfunction), pseudonormal LV filling (E/A $>$ 1, grade 2 diastolic dysfunction), and restrictive LV filling (E/A $>$ 2, grade 3 diastolic dysfunction). Farshid et al[52] reported that diastolic dysfunction is a powerful predictor of all-cause mortality in advanced CKD patients. However, several conditions, such as tachycardia, arrhythmias, and conduction system disease, will make transmitral PW Doppler parameters difficult to interpret.

The evidence of LV diastolic dysfunction provided by echocardiography is an increased LV filling pressure without other causes such as systolic dysfunction and valvular heart diseases. Currently, the most useful modality to assess LV diastolic function is a combination of mitral inflow Doppler velocity and mitral annulus tissue Doppler velocity. Average early mitral velocity (E) to early mitral annulus tissue velocity (e′) ratio has been proved to be well correlated with LV filling pressure or LA pressure. PW Doppler is performed in the apical four-chamber view to acquire mitral inflow velocities to evaluate early mitral velocity (expressed as E; Figure 1B). Tissue Doppler imaging (TDI) is performed in the apical four-chamber view to acquire mitral annular velocities, that is, the early diastolic mitral annular velocity (expressed as e′) and the late diastolic mitral annular velocity (expressed as a′; Figure 1C and D). The E/e′ ratio can be used to predict LV filling pressures,[31,41] where it is recommended to use the average e′ velocity obtained from the septal and the lateral mitral annuli. A previous study

showed that increased E/e′ indicated a more severe cardiac fibrosis and high LV filling pressure in dialysis patients.[41] However, to interpret E/e′ in these patients, it is important to consider their age, underlying CVD, and any abnormalities noted in the echocardiogram.[31] In other words, E/e′ alone should not be used as the data or the gold standard to draw the conclusion on LV diastolic function.

LV systolic function

Although most CKD patients have preserved LVEF (≥50%), reduced LVEF is well recognized as an independent prognostic predictor in CKD patients.[7,25,53] Therefore, cardiac functions in CKD patients have been studied extensively with conventional 2DE. The LV systolic function is usually evaluated using 2DE with M-mode analysis to evaluate fractional shortening, EF, and/or midwall fraction and shortening,[30] but these measurements merely provide semiquantitative evaluation and are insensitive in detecting early deterioration of cardiac function and early changes of left ventricle in CKD patients.[54]

Using pulsed TDI [i.e., systolic myocardial velocity (s′) at the septal and lateral mitral annuli; Figure 2A and B], deterioration of LV function can be detected in CKD patients.[54] Although TDI has been proven to be more accurate and sensitive than conventional echocardiography for detecting subtle systolic dysfunction, TDI-derived strain measurement has several potential pitfalls and limitations, including signal noise, artifacts, temporal resolution, and suboptimal interrogation angling.[55]

Two-dimensional speckle-tracking echocardiography imaging of myocardial deformation

Global LVEF reflects the sum of all regional shortening in the left ventricle. Methods that are able to measure LV regional function should be more sensitive than global EF for identifying systolic dysfunction. In recent years, a relatively novel modality, speckle-tracking echocardiography (STE), has been comprehensively studied to illustrate the subtle deterioration of global and regional cardiac systolic function. Speckles are natural acoustic markers, seen as small and bright elements in conventional gray-scale ultrasound images,[56] and on ultrasound images, they are distributed equally in the myocardium. The distance between selected speckles is measured simultaneously from multiple regions of interest and is a direct measure of myocardial deformation (strain). In other words, strain is the fractional change in an object's dimension in comparison to the object's original dimension. The myocardial deformation of a cardiac cycle consists of three major components, namely, longitudinal, circumferential, and radial aspects. Among these three deformation aspects, longitudinal strain is well studied and has been proven to be able to detect subtly deteriorated LV global and regional systolic functions.

LV global peak systolic longitudinal strain (GLS), obtained from 2D-STE with strain analysis (Figure 3), is the ratio of the maximal change in myocardial longitudinal length in systole to the original length. During systole, LV myocardium in the longitudinal direction shortens and GLS is represented by a negative value. The more negative the GLS value, the better the LV function. Compared with LVEF, GLS is a more sensitive, objective, and reproducible modality for assessing cardiac function. In addition, TDI-derived strain measurement has several potential pitfalls and limitations, such as signal noise, artifacts, temporal resolution, and suboptimal interrogation angling.[55,57,58] STE has also been introduced as a method for angle-independent quantification of myocardial strain.[59]

Nowadays, it is well accepted that STE can reflect regional myocardial deformation and detect small alternations in systolic function.[60] In our previous studies, we demonstrated the deterioration of LV systolic function in heart failure patients with preserved LVEF and CKD patients using STE with GLS analysis.[9,21,22,61]

Notwithstanding CAD is common in CKD patients and approximately 30–40% of ESRD patients experience ischemic events.[62,63] Accumulating evidence has revealed that STE is a powerful tool for indentifying the early changes and subtle abnormalities that develop with ischemic myocardium, and is recommended as a tool to evaluate patients with CAD.[64,65] We thus applied STE with a longitudinal strain analysis in hemodialysis patients and showed that longitudinal strain is useful for a noninvasive diagnosis of CAD in hemodialysis patients; however, measuring the level of circulating biomarkers, including cTnT, is unable to help in the screening for CAD.[16]

Despite significant advances in modern medical therapy, neither aggressive medical treatment nor multiple intervention strategies have been found to improve prognosis in ESRD patients.[66,67] This lack of documented efficacy may be attributable to the fact that interventions are studied at

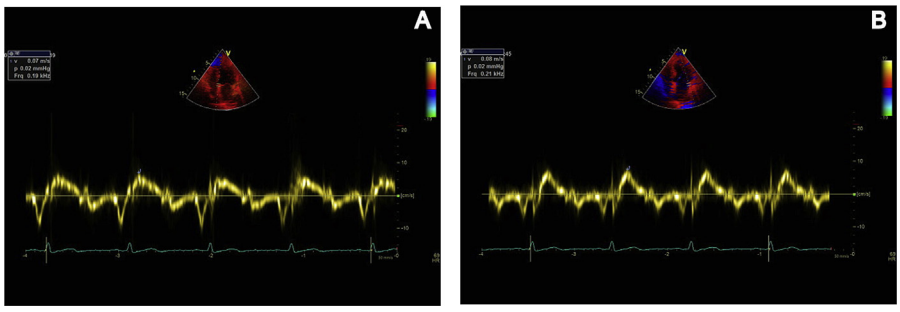


Figure 2 Pulsed tissue Doppler imaging from the (A) septal and (B) lateral mitral annuli in a chronic kidney disease patient.

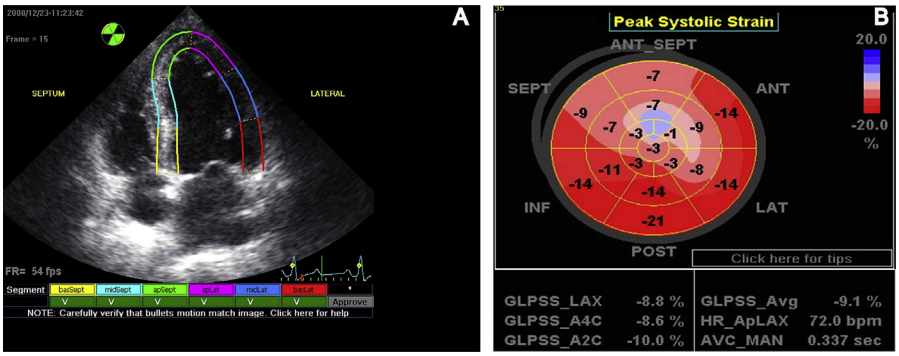


Figure 3 Processing and presentation of global left ventricular peak systolic longitudinal strain (GLS). Values of the peak systolic longitudinal strain from the apical long-axis, apical four-chamber, and apical two-chamber views were obtained from automated function imaging software. (A) Tracking quality approval screen: segments with adequate tracking are shown with a "V" mark. (B) The average value of peak systolic longitudinal strain in each segment calculated from three apical views was used to generate a parametric display, named GLS. A2C = apical two chamber; A4C = apical four chamber; apLat = apical lateral wall; apSept = apical septum; basLat = basal lateral wall; basSept = basal septum; GLPSS = global longitudinal peak systolic strain; LAX = apical long-axis; midLat = mid-lateral wall; midSept = mid-septum.

disease stages at which severe structural and functional changes have already been established. In the general population, however, GLS has been proven as a prognostic predictor.[68,69]

We also demonstrated that GLS is a powerful prognostic predictor in stable hemodialysis patients with preserved LVEF and chronic peritoneal dialysis patients.[38,70] Because a less negative GLS (GLS $\geq -15\%$) was the independent predictor of all-cause mortality and patients with a less negative GLS had a higher cardiovascular mortality rate, we highlighted the clinical application of GLS for risk assessment in clinically stable hemodialysis patients with preserved LVEF. Furthermore, the combination of GLS and interleukin-18 or cardiac troponin T may add incremental prognostic information and facilitate risk stratification for the outcomes and inform clinical decision making for stable hemodialysis patients.[9,71] However, we recognized that there is lack of strong prognostic evidence of GLS in nondialysis CKD patients. To our knowledge, only one previous study,[72] which included only 121 patients with eGFR <60, demonstrated that GLS was associated with all-cause mortality in nondialysis CKD patients. Larger prospective cohort studies are still warranted in this patient population.

A few studies indicated that myocardial strain and strain rate may provide useful information regarding diastolic function.[73–76] However, we should note that while the evaluation of diastolic function by deformation imaging might be promising, more studies are needed to confirm its incremental clinical value. Therefore, the ASE 2009 recommendation suggests that TDI-derived myocardial velocity is still the preferred methodology to evaluate LV diastolic function.[31]

Three-dimensional echocardiography (3DE) has been validated to precisely and reproducibly interpret the complex cardiac anatomy and function as well as to overcome the limitations of conventional 2DE.[77] For example, one of the major advantages of 3DE is improvement in the accuracy of cardiac chamber volume and EF measurement by diminishing geometric assumptions and errors resulting from inadequate views.[77,78] Although 3DE has been studied for years, nevertheless, it still lacks strong evidence of its applications and clinical roles in CKD patients.[79] A recent 3D-STE study demonstrated the ability of 3D-STE to detect myocardial dysfunction in ESRD patients with preserved LVEF; however, it did not prove that 3D-STE was superior to 2D-STE in detecting subclinical cardiac dysfunction. Moreover, it did not study the prognostic role of 3D-STE in CKD patients.[80]

Although there is accumulating evidence that several noninvasive markers are proved as prognostic indicators in CKD patients,[81–84] the head-to-head comparison studies between echocardiography and other noninvasive markers are limited in CKD patients. Nevertheless, we have to acknowledge that biomarkers cannot replace echocardiography but may play a complementary role in evaluating cardiovascular risk of CKD patients.[81]

Limitations

There are some limitations of echocardiography, including 2DE and 3DE, to evaluate cardiac functions.[74,75] Good image quality is essential for accurate LV quantification. Technical conditions, such as image quality, echocardiographic resolution, artifacts, may significantly affect the accuracy of cardiac measurement. In addition, although many studies indicate the possible clinical roles of echocardiography in CKD patients, there is no large cohort study to show cost effectiveness of an echocardiographic study and its impact on daily management. Therefore, it is premature to suggest routine echocardiographic study in CKD patients now, especially in those without cardiac symptom/sign. Further large-scale cohort study is necessary to validate the clinical impact and applications of echocardiographic study in CKD patients.

Conclusion

Table 1 summarizes the findings of previous studies demonstrating that echocardiographic parameters are prognostic predictors in CKD patients, which suggests that

Table 1 A summary of studies, which were cited in this review, on echocardiographic parameters as prognostic predictors in CKD patients.

Study	Studied population	Echocardiographic parameter(s)	Mean/median follow-up duration (y)	Sample size	Outcome
Foley et al[23]	ESRD	LV hypertrophy (LV mass index), LV dilatation (LV end-diastolic volume index $>$ 90 mL/m^2), & LV systolic dysfunction (FS $\leq$ 25%)	3.4	433	All-cause mortality
Wang et al[24]	Chronic PD	LV mass index	3	222	HF hospitalization due to cardiovascular congestion
Stack & Saran[35]	New ESRD	LV hypertrophy	2.0	2257	All-cause mortality
Foley et al[36]	ESRD	LV end-diastolic volume & LV mass-to-volume ratio	3.4	433	Late mortality ($>$2 y after starting dialysis therapy)
London et al[37]	HD $\geq$ 3 mo	↑ 10% LV mass	4.5	153	All-cause mortality, CV mortality
Liu et al[38]	Chronic HD	LV GLS	2.2	88	All-cause mortality, CV mortality
Barberato & Pecoits Filho[50]	Chronic HD	LAV index ($\geq$32 mL/m^2)	1.6	118	All-cause mortality & nonfatal CV events[a]
Chen et al[51]	CKD, Stages 3–5	Left atrial diameter (LAD) $>$ 4.7 cm, increased LVMI, LVEF $<$ 55%	1.1	505	CV events[b]
Farshid et al[52]	CKD, Stages 4 & 5	LV diastolic dysfunction ($\geq$Grade 2)	2.9	153	All-cause mortality, adverse CV events[c]
Liu et al[70]	Chronic PD	LV GLS	2.5	106	MAEs, MACCEs[d]
Sung et al[71]	Chronic HD	LV GLS	2.6	88	All-cause mortality
Krishnasamy et al[72]	CKD & non-CKD	LV GLS	5.2	447 (121 with eGFR $<$ 60)	All-cause mortality
Zoccali et al[84]	ESRD on regular dialysis	LVEF & LV FS at the endocardial level & at midwall	3.4	254	Fatal & nonfatal CV events[e]

CKD = chronic kidney disease; CV = cardiovascular; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EF = ejection fraction; ESRD = end-stage renal disease; FS = fractional shortening; GLS = global peak systolic longitudinal strain; HD = hemodialysis; HF = heart failure; LAD = left atrial diameter; LAV = left atrial volume; LV = left ventricular; LVMI = left ventricular mass index; MAEs = major adverse events; MACCEs = major adverse cardiovascular cerebral events; PD = peritoneal dialysis.

[a] Nonfatal CV events include new coronary event (i.e., nonfatal acute myocardial infarction or angina pectoris with coronary stenosis $>$50% on coronary angiography), ischemic or hemorrhagic stroke, and clinical diagnosis of congestive heart failure requiring hospitalization.

[b] CV events include CV death, hospitalization for unstable angina, nonfatal myocardial infarction, sustained ventricular arrhythmia, hospitalization for congestive heart failure, transient ischemia attack, and stroke.

[c] Adverse CV events include acute myocardial infarction, unstable angina, cardiac failure, cerebrovascular accident, percutaneous coronary intervention, and cardiovascular death.

[d] MACCEs include cardiovascular death, cardiac hospitalization, and stroke. MAEs are defined as all-cause mortality and MACCEs.

[e] CV events include myocardial infarction, documented angina, heart failure, transient ischemic attacks or stroke, peripheral artery disease, venous thrombosis, artery thrombosis, new onset of ECG-documented arrhythmia, and death.

echocardiography may play a pivotal role in assessing cardiac morphology and functions in CKD patients. Although STE with strain analysis and TDI can accurately access LV systolic and diastolic function, respectively, there are several pitfalls and limitations of each methodology. To interpret echocardiographic parameters precisely in CKD patients, it is important to consider patients' age, underlying comorbidities, and any abnormalities noted in the echocardiogram. In addition, further studies for developing clinical risk stratification and therapeutic strategies, possibly using echocardiogram parameters to identify high-risk patients or to follow-up the therapeutic effects, to improve CKD patients' prognosis are still warranted.

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References

1. Culleton BF, Larson MG, Wilson PW, Evans JC, Parfrey PS, Levy D. Cardiovascular disease and mortality in a community-based cohort with mild renal insufficiency. *Kidney Int* 1999;**56**:2214—9.
2. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis* 1998;**32**:S112—9.
3. Goicoechea M, de Vinuesa SG, Gomez-Campdera F, Luno J. Predictive cardiovascular risk factors in patients with chronic kidney disease (CKD). *Kidney Int Suppl* 2005:S35—8.
4. Wen CP, Cheng TY, Tsai MK, Chang YC, Chan HT, Tsai SP, et al. All-cause mortality attributable to chronic kidney disease: a prospective cohort study based on 462 293 adults in Taiwan. *Lancet* 2008;**371**:2173—82.
5. Heimdal A, Støylen A, Torp H, Skjaerpe T. Real-time strain rate imaging of the left ventricle by ultrasound. *J Am Soc Echocardiogr* 1998;**11**:1013—9.
6. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004;**351**:1296—305.
7. deFilippi C, Wasserman S, Rosanio S, Tiblier E, Sperger H, Tocchi M, et al. Cardiac troponin T and C-reactive protein for predicting prognosis, coronary atherosclerosis, and cardiomyopathy in patients undergoing long-term hemodialysis. *JAMA* 2003;**290**:353—9.
8. Akdag I, Yilmaz Y, Kahvecioglu S, Bolca N, Ercan I, Ersoy A, et al. Clinical value of the malnutrition-inflammation-atherosclerosis syndrome for long-term prediction of cardiovascular mortality in patients with end-stage renal disease: a 5-year prospective study. *Nephron Clin Pract* 2008;**108**:c99—105.
9. Liu YW, Su CT, Chang YT, Tsai WC, Su YR, Wang SP, et al. Elevated serum interleukin-18 level is associated with all-cause mortality in stable hemodialysis patients independently of cardiac dysfunction. *PLoS One* 2014;**9**:e89457.
10. Baigent C, Burbury K, Wheeler D. Premature cardiovascular disease in chronic renal failure. *Lancet* 2000;**356**:147—52.
11. Hayashi SY, Brodin LA, Alvestrand A, Lind B, Stenvinkel P, Mazza do Nascimento M, et al. Improvement of cardiac function after haemodialysis. Quantitative evaluation by colour tissue velocity imaging. *Nephrol Dial Transplant* 2004;**19**:1497—506.
12. Lin CM, Yang MC, Hwang SJ, Sung JM. Progression of stages 3b-5 chronic kidney disease—preliminary results of Taiwan national pre-ESRD disease management program in Southern Taiwan. *J Formos Med Assoc* 2013;**112**:773—82.
13. Huang YY, Lin KD, Jiang YD, Chang CH, Chung CH, Chuang LM, et al. Diabetes-related kidney, eye, and foot disease in Taiwan: an analysis of the nationwide data for 2000—2009. *J Formos Med Assoc* 2012;**111**:637—44.
14. Chang FC, Chiang WC, Tsai MH, Chou YH, Pan SY, Chang YT, et al. Angiopoietin-2-induced arterial stiffness in CKD. *J Am Soc Nephrol* 2014;**25**:1198—209.
15. Chen PM, Lai TS, Chen PY, Lai CF, Wu V, Chiang WC, et al. Renoprotective effect of combining pentoxifylline with angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker in advanced chronic kidney disease. *J Formos Med Assoc* 2014;**113**:219—26.
16. Liu YW, Su CT, Wang SP, Yang CS, Huang JW, Hung KY, et al. Application of speckle-tracking echocardiography in detecting coronary artery disease in patients with maintenance hemodialysis. *Blood Purif* 2011;**32**:38—42.
17. Wase A, Basit A, Nazir R, Jamal A, Shah S, Khan T, et al. Impact of chronic kidney disease upon survival among implantable cardioverter-defibrillator recipients. *J Interv Card Electrophysiol* 2004;**11**:199—204.
18. McCullough PA. Cardiovascular disease in chronic kidney disease from a cardiologist's perspective. *Curr Opin Nephrol Hypertens* 2004;**13**:591—600.
19. Best PJ, Reddan DN, Berger PB, Szczech LA, McCullough PA, Califf RM. Cardiovascular disease and chronic kidney disease: insights and an update. *Am Heart J* 2004;**148**:230—42.
20. McCullough PA, Sandberg KR. Chronic kidney disease and sudden death: strategies for prevention. *Blood Purif* 2004;**22**:136—42.
21. Liu YW, Su CT, Chou CC, Wang SPH, Yang CS, Huang YY, et al. Association of subtle left ventricular systolic dysfunction with elevated cardiac troponin T in asymptomatic hemodialysis patients with preserved left ventricular ejection fraction. *Acta Sin Cardiol* 2012;**28**:95—102.
22. Liu YW, Su CT, Huang YY, Yang CS, Huang JW, Yang MT, et al. Left ventricular systolic strain in chronic kidney disease and hemodialysis patients. *Am J Nephrol* 2011;**33**:84—90.
23. Foley RN, Parfrey PS, Harnett JD, Kent GM, Martin CJ, Murray DC, et al. Clinical and echocardiographic disease in patients starting end-stage renal disease therapy. *Kidney Int* 1995;**47**:186—92.
24. Wang AY, Lam CW, Yu CM, Wang M, Chan IH, Lui SF, et al. Troponin T, left ventricular mass, and function are excellent predictors of cardiovascular congestion in peritoneal dialysis. *Kidney Int* 2006;**70**:444—52.
25. Sharma R, Gaze DC, Pellerin D, Mehta RL, Gregson H, Streather CP, et al. Cardiac structural and functional abnormalities in end stage renal disease patients with elevated cardiac troponin T. *Heart* 2006;**92**:804—9.
26. Pennell DJ, Sechtem UP, Higgins CB, Manning WJ, Pohost GM, Rademakers FE, et al. Clinical indications for cardiovascular magnetic resonance (CMR): consensus Panel report. *Eur Heart J* 2004;**25**:1940—65.
27. Flett AS, Westwood MA, Davies LC, Mathur A, Moon JC. The prognostic implications of cardiovascular magnetic resonance. *Circ Cardiovasc Imaging* 2009;**2**:243—50.
28. Perazella MA. Current status of gadolinium toxicity in patients with kidney disease. *Clin J Am Soc Nephrol* 2009;**4**:461—9.
29. Bennett CL, Qureshi ZP, Sartor AO, Norris LB, Murday A, Xirasagar S, et al. Gadolinium-induced nephrogenic systemic fibrosis: the rise and fall of an iatrogenic disease. *Clin Kidney J* 2012;**5**:82—8.
30. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005;**18**:1440—63.
31. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *J Am Soc Echocardiogr* 2009;**22**:107—33.
32. Park M, Hsu CY, Li Y, Mishra RK, Keane M, Rosas SE, et al. Associations between kidney function and subclinical cardiac abnormalities in CKD. *J Am Soc Nephrol* 2012;**23**:1725—34.
33. Cai QZ, Lu XZ, Lu Y, Wang AY. Longitudinal changes of cardiac structure and function in CKD (CASCADE study). *J Am Soc Nephrol* 2014;**25**:1599—608.

34. Parfrey PS, Foley RN. The clinical epidemiology of cardiac disease in chronic renal failure. *J Am Soc Nephrol* 1999;**10**:1606—15.
35. Stack AG, Saran R. Clinical correlates and mortality impact of left ventricular hypertrophy among new ESRD patients in the United States. *Am J Kidney Dis* 2002;**40**:1202—10.
36. Foley RN, Parfrey PS, Harnett JD, Kent GM, Murray DC, Barré PE. The prognostic importance of left ventricular geometry in uremic cardiomyopathy. *J Am Soc Nephrol* 1995;**5**:2024—31.
37. London GM, Pannier B, Guerin AP, Blacher J, Marchais SJ, Darne B, et al. Alterations of left ventricular hypertrophy in and survival of patients receiving hemodialysis: follow-up of an interventional study. *J Am Soc Nephrol* 2001;**12**:2759—67.
38. Liu YW, Su CT, Sung JM, Wang SP, Su YR, Yang CS, et al. Association of left ventricular longitudinal strain with mortality among stable hemodialysis patients with preserved left ventricular ejection fraction. *Clin J Am Soc Nephrol* 2013;**8**:1564—74.
39. Shroff GR, Herzog CA. Echocardiography: providing additional insights into cardiovascular structural and functional abnormalities in advanced CKD. *Clin J Am Soc Nephrol* 2013;**8**:339—41.
40. Pecoits-Filho R, Barberato SH. Echocardiography in chronic kidney disease: diagnostic and prognostic implications. *Nephron Clin Pract* 2010;**114**:c242—7.
41. Su CT, Liu YW, Lin JW, Chen SI, Yang CS, Chen JH, et al. Increased procollagen type I C-terminal peptide levels indicate diastolic dysfunction in end-stage renal disease patients undergoing maintenance dialysis therapy. *J Am Soc Echocardiogr* 2012;**25**:895—901.
42. Gill RM, Jones BD, Corbly AK, Wang J, Braz JC, Sandusky GE, et al. Cardiac diastolic dysfunction in conscious dogs with heart failure induced by chronic coronary microembolization. *Am J Physiol Heart Circ Physiol* 2006;**291**:H3154—8.
43. Roongsritong C, Sadhu A, Pierce M, Raj R, Simoni J. Plasma carboxy-terminal peptide of procollagen type I is an independent predictor of diastolic function in patients with advanced systolic heart failure. *Congest Heart Fail* 2008;**14**:302—6.
44. Querejeta R, Varo N, López B, Larman M, Artiñano E, Etayo JC, et al. Serum carboxy-terminal propeptide of procollagen type I is a marker of myocardial fibrosis in hypertensive heart disease. *Circulation* 2000;**101**:1729—35.
45. Maceira AM, Barba J, Varo N, Beloqui O, Díez J. Ultrasonic backscatter and serum marker of cardiac fibrosis in hypertensives. *Hypertension* 2002;**39**:923—8.
46. Ho CY, López B, Coelho-Filho OR, Lakdawala NK, Cirino AL, Jarolim P, et al. Myocardial fibrosis as an early manifestation of hypertrophic cardiomyopathy. *N Engl J Med* 2010;**363**:552—63.
47. Ihm SH, Youn HJ, Shin DI, Jang SW, Park CS, Kim PJ, et al. Serum carboxy-terminal propeptide of type I procollagen (PIP) is a marker of diastolic dysfunction in patients with early type 2 diabetes mellitus. *Int J Cardiol* 2007;**122**:e36—8.
48. Tsai WC, Lin CC, Chen JY, Huang YY, Lee CH, Li WT, et al. Association of adiponectin with procollagen type I carboxyterminal propeptide in non-diabetic essential hypertension. *Blood Press* 2008;**17**:233—8.
49. Brutsaert DL, Sys SU, Gillebert TC. Diastolic failure: pathophysiology and therapeutic implications. *J Am Coll Cardiol* 1993;**22**:318—25.
50. Barberato SH, Pecoits Filho R. Prognostic value of left atrial volume index in hemodialysis patients. *Arq Bras Cardiol* 2007;**88**:643—50 [Article in English, Portuguese].
51. Chen SC, Chang JM, Liu WC, Huang JC, Tsai JC, Lin MY, et al. Echocardiographic parameters are independently associated with increased cardiovascular events in patients with chronic kidney disease. *Nephrol Dial Transplant* 2012;**27**:1064—70.
52. Farshid A, Pathak R, Shadbolt B, Arnolda L, Talaulikar G. Diastolic function is a strong predictor of mortality in patients with chronic kidney disease. *BMC Nephrol* 2013;**14**:280.
53. Wang AY, Lam CW, Wang M, Chan IH, Lui SF, Zhang Y, et al. Diagnostic potential of serum biomarkers for left ventricular abnormalities in chronic peritoneal dialysis patients. *Nephrol Dial Transplant* 2009;**24**:1962—9.
54. Edwards NC, Hirth A, Ferro CJ, Townend JN, Steeds RP. Subclinical abnormalities of left ventricular myocardial deformation in early-stage chronic kidney disease: the precursor of uremic cardiomyopathy? *J Am Soc Echocardiogr* 2008;**21**:1293—8.
55. Storaa C, Aberg P, Lind B, Brodin LA. Effect of angular error on tissue Doppler velocities and strain. *Echocardiography* 2003;**20**:581—7.
56. Leitman M, Lysyansky P, Sidenko S, Shir V, Peleg E, Binenbaum M, et al. Two-dimensional strain-a novel software for real-time quantitative echocardiographic assessment of myocardial function. *J Am Soc Echocardiogr* 2004;**17**:1021—9.
57. Herbots L, Maes F, D'hooge J, Claus P, Dymarkowski S, Mertens P, et al. Quantifying myocardial deformation throughout the cardiac cycle: a comparison of ultrasound strain rate, grey-scale M-mode and magnetic resonance imaging. *Ultrasound Med Biol* 2004;**30**:591—8.
58. Behar V, Adam D, Lysyansky P, Friedman Z. The combined effect of nonlinear filtration and window size on the accuracy of tissue displacement estimation using detected echo signals. *Ultrasonics* 2004;**41**:743—53.
59. Bohs LN, Trahey GE. A novel method for angle independent ultrasonic imaging of blood flow and tissue motion. *IEEE Trans Biomed Eng* 1991;**38**:280—6.
60. Edvardsen T, Helle-Valle T, Smiseth OA. Systolic dysfunction in heart failure with normal ejection fraction: speckle-tracking echocardiography. *Prog Cardiovasc Dis* 2006;**49**:207—14.
61. Liu YW, Tsai WC, Su CT, Lin CC, Chen JH. Evidence of left ventricular systolic dysfunction detected by automated function imaging in patients with heart failure and preserved left ventricular ejection fraction. *J Card Fail* 2009;**15**:782—9.
62. Wardle EN. Premature cardiovascular disease and chronic renal failure. *Lancet* 2000;**356**:854—5.
63. Edwards NC, Steeds RP, Ferro CJ, Townend JN. The treatment of coronary artery disease in patients with chronic kidney disease. *QJM* 2006;**99**:723—36.
64. Perk G, Kronzon I. Non-Doppler two dimensional strain imaging for evaluation of coronary artery disease. *Echocardiography* 2009;**26**:299—306.
65. Tsai WC, Liu YW, Huang YY, Lin CC, Lee CH, Tsai LM. Diagnostic value of segmental longitudinal strain by automated function imaging in coronary artery disease without left ventricular dysfunction. *J Am Soc Echocardiogr* 2010;**23**:1183—9.
66. Isbel NM, Haluska B, Johnson DW, Beller E, Hawley C, Marwick TH. Increased targeting of cardiovascular risk factors in patients with chronic kidney disease does not improve atheroma burden or cardiovascular function. *Am Heart J* 2006;**151**:745—53.
67. Wanner C, Krane V, März W, Olschewski M, Mann JF, Ruf G, et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med* 2005;**353**:238—48.
68. Stanton T, Leano R, Marwick TH. Prediction of all-cause mortality from global longitudinal speckle strain: comparison with ejection fraction and wall motion scoring. *Circ Cardiovasc Imaging* 2009;**2**:356—64.
69. Mignot A, Donal E, Zaroui A, Reant P, Salem A, Hamon C, et al. Global longitudinal strain as a major predictor of cardiac events in patients with depressed left ventricular function: a multicenter study. *J Am Soc Echocardiogr* 2010;**23**:1019—24.
70. Liu YW, Tseng CC, Su CT, Chang YT, Chen JY, Chen LY, et al. The prognostic value of left ventricular global peak systolic

longitudinal strain in chronic peritoneal dialysis patients. *IJC Heart Vasc* 2014;**5**:1—8.
71. Sung JM, Su CT, Chang YT, Su YR, Tsai WC, Wang SP, et al. Independent value of cardiac troponin T and left ventricular global longitudinal strain in predicting all-cause mortality among stable hemodialysis patients with preserved left ventricular ejection fraction. *Biomed Res Int* 2014;**2014**:217290.
72. Krishnasamy R, Isbel NM, Hawley CM, Pascoe EM, Leano R, Haluska BA, et al. The association between left ventricular global longitudinal strain, renal impairment and all-cause mortality. *Nephrol Dial Transplant* 2014;**29**:1218—25.
73. Tsai WC, Liu YW, Chen JY, Huang YY, Shih JY, Tsai LM, et al. Postsystolic strain index is associated with delayed diastolic lengthening and diastolic dysfunction of the left ventricle in untreated hypertension. *J Hypertens* 2012;**30**:787—93.
74. Pislaru C, Bruce CJ, Anagnostopoulos PC, Allen JL, Seward JB, Pellikka PA, et al. Ultrasound strain imaging of altered myocardial stiffness: stunned versus infarcted reperfused myocardium. *Circulation* 2004;**109**:2905—10.
75. Abraham TP, Belohlavek M, Thomson HL, Pislaru C, Khandheria B, Seward JB, et al. Time to onset of regional relaxation: feasibility, variability and utility of a novel index of regional myocardial function by strain rate imaging. *J Am Coll Cardiol* 2002;**39**:1531—7.
76. Wang J, Khoury DS, Thohan V, Torre-Amione G, Nagueh SF. Global diastolic strain rate for the assessment of left ventricular relaxation and filling pressures. *Circulation* 2007;**115**:1376—83.
77. Hung J, Lang R, Flachskampf F, Shernan SK, McCulloch ML, Adams DB, et al. 3D echocardiography: a review of the current status and future directions. *J Am Soc Echocardiogr* 2007;**20**:213—33.
78. Badano LP, Boccalini F, Muraru D, Bianco LD, Peluso D, Bellu R, et al. Current clinical applications of transthoracic three-dimensional echocardiography. *J Cardiovasc Ultrasound* 2012;**20**:1—22.
79. Glassock RJ, Pecoits-Filho R, Barberato SH. Left ventricular mass in chronic kidney disease and ESRD. *Clin J Am Soc Nephrol* 2009;**4**:S79—91.
80. Chen R, Wu X, Shen LJ, Wang B, Ma MM, Yang Y, et al. Left ventricular myocardial function in hemodialysis and nondialysis uremia patients: a three-dimensional speckle-tracking echocardiography study. *PLoS One* 2014;**9**:e100265.
81. Wang AY, Lai KN. Use of cardiac biomarkers in end-stage renal disease. *J Am Soc Nephrol* 2008;**19**:1643—52.
82. Kim JK, Song YR, Kim MG, Kim HJ, Kim SG. Clinical significance of subclinical carotid atherosclerosis and its relationship with echocardiographic parameters in non-diabetic chronic kidney disease patients. *BMC Cardiovasc Disord* 2013;**13**:96.
83. Chen SC, Su HM, Tsai YC, Huang JC, Chang JM, Hwang SJ, et al. Framingham risk score with cardiovascular events in chronic kidney disease. *PLoS One* 2013;**8**:e60008.
84. Zoccali C, Benedetto FA, Mallamaci F, Tripepi G, Giacone G, Cataliotti A, et al. Prognostic value of echocardiographic indicators of left ventricular systolic function in asymptomatic dialysis patients. *J Am Soc Nephrol* 2004;**15**:1029—37.