Assessing Heart Geometry and Function in Asymptomatic Patients with Chronic Kidney Disease

Khajalia S.[1], Pagava Z.[2], Gaprindashvili T.[2], Botchorishvili I.[2]

Abstract

Background: Heart-kidney interaction plays a crucial role in the development of chronic kidney disease and its cardiovascular complications, commonly referred to as cardiorenal syndrome. In cardiorenal syndrome, chronic kidney disease contributes to cardiovascular dysfunction through mechanisms like pressure overload, volume overload, and non-hemodynamic factors. These factors lead to myocardial remodeling, left ventricular hypertrophy, diastolic dysfunction, and myocardial fibrosis, resulting in increased left ventricular filling pressures and impaired cardiac function.
Aim: Incorporating global longitudinal strain measurements into clinical practice, alongside traditional echocardiographic assessments, can improve the early detection and management of cardiorenal syndrome, allowing for timely interventions that reduce the risk of heart failure and cardiovascular events. Early identification and monitoring of global longitudinal strain may help mitigate long-term cardiovascular risk and improve patient outcomes.
Methods: **:** Echocardiography, particularly through the use of global longitudinal strain, has become a valuable tool for assessing myocardial dysfunction in chronic kidney disease patients. Global longitudinal strain is a sensitive biomarker for early detection of subclinical cardiac dysfunction, even in patients with preserved ejection fraction and no overt cardiovascular symptoms.
Results: Speckle-tracking echocardiography, particularly global longitudinal strain, has proven valuable in detecting early myocardial dysfunction in CKD patients, offering critical prognostic insights. Early detection of left ventricular abnormalities through global longitudinal strain can guide interventions to prevent progression to severe cardiovascular outcomes. **Conclusions**: Managing chronic kidney disease and cardiovascular disease together, with advanced diagnostic techniques, is essential for improving patient outcomes, highlighting the need for a multidisciplinary approach to address this complex health challenge. **(TCM-GMJ June 2025; 10 (1): P65-P71)**

Keywords: Heart-kidney interaction, Chronic Kidney Disease, Echocardiography, Cardiorenal Syndrome, Global Longitudinal strain

.

Introduction

The interaction between the heart and kidneys were mentioned even in ancient times, including the Old Testament and the Egyptian 'Book of the Dead'. An English pathologist, Richard Bright, described in 1836 cardiac enlargement in patients with advanced renal diseases who might have been hypertensive. In 1913, Thomas Lewis, was the first to use the term 'cardiorenal patients'. By the mid-20th century when both cardiovascular and renal functions were measurable, it was noted that some patients with heart failure had impaired estimated renal glomerular filtration rates.

Patients with chronic kidney disease (CKD) exhibit a highly increased risk of cardiovascular (CV) morbidity and mortality compared to the general population. CV disease is considered to be responsible for 50–60% of all deaths in patients with CKD. CKD patients experience angina or myocardial infarction symptoms in an atypical manner, which considerably complicates the diagnosis of CV disease in this high-risk patient group. However, concerns about radiocontrast nephropathy and toxicity of gadolinium-containing contrast agents often limit an adequate work-up of suspected CV disease in CKD patients. Therefore, non-invasive and non-contrast based diagnostic methods that can detect early structural and functional myocardial abnormalities and that can identify patients at risk for CV disease are necessary to initiate adequate diagnostic, preventive, and therapeutic measures.

Chronic kidney disease is associated with structural and functional left ventricular remodeling as a consequence of pressure and volume overload and nonhemodynamic factors. Pressure overload is the result of chronic hypertension and vascular stiffness, whereas anemia, arte-

From the [1]Ivane Javakhishvili Tbilisi State University, Georgia; [2]Bokhua Memorial Cardiovascular Center;
Received March 18, 2025; accepted April 29, 2025.
Address requests to: Khajalia Sergo
E-mail: s_khajalia@yahoo.com
Copyright © 2025 Translational and Clinical Medicine-Georgian Medical Journal

riovenous fistulas, and sodium and water retention lead to volume overload. To keep left ventricular wall stress close to normal, the left ventricle responds to pressure and volume overload with hypertrophy and dilatation. As left ventricular hypertrophy progresses, the interstitial space also increases with accumulation of collagen potentially causing a reduction in contractility. Furthermore, nonhemodynamic factors associated with CKD such as inappropriate renin -angiotensin-aldosterone system activation, oxidative stress, inflammation, and stimulation of pro-hypertrophic and profibrogenic factors also contribute to left ventricular remodeling. These structural changes cause impaired left ventricular contractility, which can be detected with left ventricular global longitudinal strain.

Methods

The Relationship between Chronic Kidney Disease and Cardiovascular Disease

Chronic kidney disease (CKD) is a progressive disease which affects approximately 13% of the world's population. Over time, it can cause renal dysfunction and progression to end-stage kidney disease and cardiovascular disease. The diagnosis of CKD is made by laboratory testing, most often by estimating glomerular filtration rate (eGFR) or by testing urine for the presence of albumin or protein (or a combination of these). To differentiate chronic kidney disease from conditions such as acute kidney injury or from transient fluctuations in kidney function unrelated to kidney damage, the standard definition includes a so-called "chronicity criterion" (i.e., that the low eGFR or elevated urine albumin should be detectable for at least 90 days, requiring the presence of repeated measurements over time).

Chronic kidney disease involves both nonmodifiable (e.g. older age, family history and ethnicity) and modifiable risk factors (e.g. Type 2 diabetes mellitus, arterial hypertension and dyslipidemia) which are responsible for the initiation of early CKD, its progression (stage 3–5) and end stage kidney disease. In early stages of the disease (stage 1–2), factors such as hypertension, obesity and Type 2 diabetes mellitus, can trigger kidney function impairment. This causes glomerular/interstitial damage and results in impaired glomerular filtration, leading to decreased eGFR and increased albuminuria. At this stage, even though clinical symptoms do not present, the presence of additional risk factors (e.g. smoking, dyslipidemia, cardiovascular disease), may accelerate CKD progression and result in end stage kidney disease.

As the disease progresses, the risk of cardiovascular disease is markedly increased, such that 50% of patients with late-stage CKD, stage 4–5, have cardiovascular disease. The risk of atrial fibrillation and acute coronary syndrome is doubled in patients with eGFR < 60 mL/min per 1.73 m^2. The incidence of heart failure is also threefold greater in patients with eGFR <60 mL/min per 1.73 m^2 compared with >90 mL/min per 1.73 m^2 (1).

Chronic kidney disease exposes the heart to three major mechanisms that facilitate the development of cardiomyopathy and induce LV failure: pressure overload, volume overload, and CKD-associated non-hemodynamic factors that alter the myocardium. Pressure overload is largely the result of long-standing hypertension and vascular stiffness. Increased LV wall stress (from pressure and volume overload) fuels changes in the composition and function of the myocardium, and this process is accentuated by CKD-associated abnormalities (6). Beyond hemodynamic factors, inappropriate activation of the renin–angiotensin system, oxidative stress, inflammation, and stimulation of pro-hypertrophic and profibrogenic factors (cardiotrophin-1, galectin-3, transforming growth factor-b, fibroblast growth factor-23) may be relevant.

CKD progression is accompanied by progressive left ventricular hypertrophy and diastolic dysfunction. Left ventricular diastolic dysfunction is frequent among CKD patients and is associated with the risk of congestive heart failure and increased mortality. Myocardial fibrosis results from an imbalance between exaggerated collagen synthesis and unchanged or depressed collagen degradation. In CKD patients, it is a major determinant of left ventricular stiffness, increased filling pressure, and disturbances in diastolic filling. In CKD patients, resting left ventricular systolic function is usually normal or even hyperdynamic.

Cardiorenal Syndrome

In 1998, the US National Kidney Foundation published a detailed monograph on this subject that emphasized three points: (i) an inverse association exists between eGFR and adverse cardiac events; (ii) pa- tients with chronic kidney disease (CKD) are at high risk of developing atherosclerotic cardiovascular disease, and/or heart failure; and (iii) evaluation of patients with or at risk of cardiovascular disease should include measurements of eGFR and of the urine albumin/creatinine ratio. In an effort to explore further this bidirectional interplay between the two organ systems, the National Heart, Lung and Blood Institute established a 'Working Group on Cardiorenal Connections' and the American Heart Association a 'Council on the Kidney in Cardiovascular Disease.' In 2004, the combination of the disorders was termed the 'cardiorenal syndrome' by Heywood, who defined it as a 'moderate or greater renal dysfunction that exists or devel- ops in patients with HF.' Ronco *et al.* subdivided CRS into five subgroups, identifying the precipitating organ (heart or kidney) and the temporal pattern (acute or chronic).

A typical clinical example of type 1 cardiorenal syndrome includes acute decompensated heart failure, which leads to acute kidney injury (AKI) or acute coronary syndrome resulting in cardiogenic shock and leading to AKI. Traditionally, the pathophysiology was believed to be that the decreased cardiac output from heart failure was initially contributing to worsening renal function due to decreased effective circulating volume. However, more recently, evidence has made apparent the fact that venous congestion plays a significant role, and it is thought to be the primary hemodynamic precipitant for deterioration in renal function (10).

Cardiorenal syndrome type 2 (CRS-2) is identified by a persistent cardiac dysfunction that causes to chronic kid-

ney disease over time. Heart failure with preserved and reduced ejection fraction, congenital heart disease, atrial fibrillation and ischemic heart disease are all underlying diseases in this case. CKD must appear secondarily to chronic heart failure to be classified as CRS-2 (11).

Type 3 cardiorenal syndrome is an acute and abrupt deterioration in renal function leading to acute cardiac dysfunction, such as acute kidney injury leading to volume overload, inflammatory surge, and metabolic disturbances leading to heart failure, arrhythmia, or ischemia.

Cardiorenal syndrome type 4 is defined on the basis of chronic kidney disease as the cause of cardiac dysfunction. Vasoconstriction, sodium and water reabsorption, and oxidative stress, renin-angiotensin-aldosterone system and sympathetic nervous system activation can contribute to CRS-4.

Type 5 cardiorenal syndrome is characterized by a systemic disorder or acute systemic insult resulting in simultaneous cardiac and renal dysfunction. In the setting of sepsis, inflammation and microvasculature alterations can result in alteration of organ function leading to cardiac and renal involvement. Many systemic conditions can lead to CRS type 5, including sepsis, amyloidosis, diabetes, and systemic lupus erythematosus.

Overall, the breadth and complexity of cardiorenal syndrome requires the knowledge and skills of both nephrology and cardiology, hence the need for nephrocardiologists (or cardionephrologists).

An Overview of Cardiovascular-Kidney-Metabolic Syndrome

It is well established that patients with CRS are more likely to die of a cardiac event than from kidney failure, and the severity of CRS is influenced by the presence of additional underlying conditions. The most frequent of these, type 2 diabetes, greatly increased the risk of the development and severity of cardiac and renal disorders as well as of their combination in CRS., Other common risk factors that occur in both CVD and CKD include visceral obesity, the metabolic syndrome, dyslipidemias, hypertension, and pro- thrombotic phenotypes. These metabolic disorders can cause oxidative stress, endothelial dysfunction, inflammation, arterial plaques, and thrombosis. Given the importance of this, in 2023, the American heart association expanded cardiovascular and kidney risk factors into a new group of syndromes, the cardiovascular–kidney–metabolic (CKM) syndromes. Cardiovascular-kidney-metabolic (CKM) syndrome is a systemic disorder characterized by pathophysiological interactions among metabolic risk factors, CKD, and the cardiovascular system leading to multiorgan dysfunction and a high rate of adverse cardiovascular outcomes. CKM syndrome includes both individuals at risk for cardiovascular disease (CVD) and individuals with existing CVD.

The CKM staging model emphasizes the progressive pathophysiology of CKM syndrome, underscores the importance of early detection of CKM-related changes to support prevention efforts, and highlights the stepwise increase in absolute CVD risk associated with later stages (13).

Stage 0 is defined as the absence of CKM risk factors with normal BMI and waist circumference, normoglycemia, normotension and a normal lipid profile.

Stage 1 is defined as having excess weight (body mass index ≥25 kg/m^2), abdominal obesity (waist circumference ≥88 cm in women and ≥102 cm in men), or dysfunctional adipose tissue (clinically manifest as impaired glucose tolerance or prediabetes) without the presence of other metabolic risk factors or CKD.

Stage 2 of CKM syndrome is diagnosed in case of the presence of metabolic risk factors (hypertriglyceridemia [≥135 mg/dL], hypertension [stages 1 and 2], Metabolic syndrome, diabetes), moderate- to high-risk CKD, or both.

In stage 3 CKM syndrome there is subclinical CVD among individuals with excess/dysfunctional adiposity, metabolic risk factors, or CKD. This includes imaging markers of subclinical atherosclerotic CVD (an increased coronary artery calcium score on cardiac computed tomography but also potentially reflected by nonobstructive coronary artery disease on coronary angiography or by subclinical peripheral artery disease) or subclinical heart failure (elevation in cardiac biomarkers) or abnormal cardiovascular structure or function on myocardial imaging in the absence of clinical symptoms.

Stage 4 CKM syndrome is defined as clinical cardiovascular disease among individuals with excess/ dysfunctional adiposity, other metabolic risk factors, or CKD. This stage is further divided into 4a (without kidney failure) and 4b (with kidney failure).

'*The Butterfly Effect'- A New Concept in Cardiorenal Syndrome*

In 2024, Zoccali and colleagues, with Zannad and Rossignol among them, argued that the term "Cardiorenal Syndrome" is no longer suitable and advocated for a shift toward the phrase "Chronic Cardiovascular and Kidney Disorder". Furthermore, the new concept called the "butterfly effect", encompasses not only the chronic aspects of the disorder, but also incorporates the impact of acute organ insults that may lead to the development of long-term significant organ damage. The butterfly effect, in this context, suggests that an acute, often resolvable alteration in one organ (either cardiac or renal) can trigger significant long-term effects (14).

The cardiorenal butterfly effect is not a necessary condition for the development of clinically significant cardiovascular and kidney outcomes because of the following: It is not required, as CKD or HF can evolve into CRS without an acute insult. However, it is important to acknowledge that even a reversible, acute renal or cardiac insult could have underappreciated long-term consequences.

Heart-kidney interaction

Left ventricular hypertrophy is highly prevalent in the non-dialysis CKD population from the early stages of renal disease. Paoletti et al. enrolled 445 patients with hypertension and CKD stages 2–5 in two academic nephrol-

ogy clinics who underwent echocardiography and ambulatory BP monitoring. This study provided first-time evidence that, in patients with non-dialysis CKD, the presence of left ventricular hypertrophy, portends a poor renal and cardiovascular long–term outcomes. In fact, both concentric and eccentric left ventricular hypertrophies did associate with a two- to threefold increase in the risk of cardiovascular event, end stage renal disease onset, and all -cause mortality.

The study conducted by Jain and colleagues sought to determine the association between renal function and diastolic dysfunction in subjects with preserved ejection fraction. The presence of diastolic dysfunction was associated with long-term morbidity and mortality. In addition, they reported for the first time that abnormal diastolic function was associated with increased progression to death, heart failure, and hospitalization irrespective of glomerular filtration rate.

Assessment of left ventricular filling pressure (using E/e' ratio) after exercise has been useful in unmasking latent diastolic dysfunction. Few studies, however, have evaluated the utility of resting and exercise E/e' in patients with chronic kidney disease and their correlation with exercise capacity. One of them observed that patients with raised E/e' have a significantly higher incidence for the composite endpoint of cardiovascular death and major adverse cardiovascular events. Additionally, the same study has illustrated the important negative effects of left ventricular hypertrophy, diastolic dysfunction, and elevated filling pressures, which all limit exercise capacity and confer an increased risk of morbidity and mortality. Hence, these parameters need to be closely monitored, with appropriate risk factor control and lifestyle changes, to prevent their development during the course of CKD.

CKD patients suffer more from valve disease. Samad et al. found higher odds of aortic stenosis and mitral regurgitation among those with versus without chronic kidney disease. A higher prevalence of mitral regurgitation likely reflects structural changes in the mitral valve apparatus: restricted motion of the annulus, leaflets, or chordae caused by calcification and reduced left ventricular wall motion related to coronary artery disease among CKD patients. The higher prevalence of aortic stenosis in patients undergoing hemodialysis is well known and previously thought to be related to progressive valve calcification of the cardiac skeleton and valve leaflets—a result of altered or deranged calcium phosphate metabolism and hypertension in end-stage renal disease.

Results and discussion

Efficacy of Speckle-tracking Echocardiography in Heart Diseases

Myocardial strain is a dimensionless variable that represents the change in length between two points over the cardiac cycle. Strain imaging enables the assessment of the spatial components of left ventricular contraction that are the result of the changing orientation of myocardial fibres between the sub-endocardium and sub-epicardium. Although global longitudinal strain (GLS) and ejection fraction are highly correlated, they measure different aspects of the myocardial deformation. Ejection fraction predominantly quantifies radial contraction and global longitudinal strain represents the function of subendocardial longitudinal myocardial fibres that are more sensitive to reduced coronary perfusion and increased wall stress.

Global longitudinal strain is impaired in heart failure patients with preserved ejection fraction. This relates to the fact that subendocardial function is likely to be impaired in diastolic heart failure patients while epicardial/transmural function remains preserved which explains the preserved left ventricular ejection fraction. Abnormal longitudinal function in this cohort can be detected at an earlier stage by examining subendocardial function by GLS measurement. This suggests that GLS could act as more sensitive prognostic biomarker for heart failure patients with preserved ejection fraction.

Whilst more straightforward in patients with heart failure with reduced ejection fraction (HF-REF), the diagnosis and risk stratification of patients presenting with shortness of breath and truly preserved ejection fraction remains a challenge due to the heterogeneity of phenotypes and typical presence of contributing co-morbidities. Diagnostic criteria include diastolic parameters, left atrial size, natriuretic peptide concentration, and more recently GLS. Reduction in GLS may be one of the earliest signs, even before the detection of diastolic dysfunction at rest. Amongst asymptomatic patients with hypertension and diabetes mellitus at risk of developing heart failure with preserved ejection fraction, reduction in GLS is common. A study of asymptomatic adults with type 2 diabetes mellitus demonstrated that 45% had reduced GLS and this was associated with adverse outcomes over follow-up.

The prognostic importance of GLS has also been confirmed in both types of heart failure. A recent large study in over 4000 patients with acute heart failure confirmed increased mortality with reduced GLS that was consistent across different sub-groups of left ventricular ejection fraction. Global longitudinal strain had superior prognostic value compared with left ventricular ejection fraction. In a meta-analysis of studies, across a spectrum of cardiac conditions including heart failure, GLS appeared to have superior prognostic value compared with left ventricular ejection fraction.

Echocardiography using speckle-tracking longitudinal strain can be used for differential diagnosis of left ventricular hypertrophy caused by arterial hypertension, hypertrophic cardiomyopathy, cardiac amyloidosis, Fabry disease and some other abnormalities.

Global longitudinal strain(GLS) helps to unmask early subclinical left ventricular systolic dysfunction in patients with arterial hypertension. The basal septum is the first segment to undergo changes under the influence of pressure overload, and GLS is further reduced at this site.

In patients with hypertrophic cardiomyopathy, LV longitudinal myocardial function is typically reduced at the site of hypertrophy, especially in the region of the interventricular septum. These patients were found to have similar left ventricular ejection fraction but worse global

longitudinal strain compared to healthy individuals, and those with ventricular arrhythmias showed worse GLS than those without them. Therefore, GLS is an appropriate parameter for evaluating left ventricular systolic function in hypertrophic cardiomyopathy and may improve risk stratification of ventricular arrhythmia for such patients.

In cardiac amyloidosis a longitudinal strain gradient with preserved systolic strain at apical segments and significantly reduced systolic strain at mid and basal segments is consistently observed. This pattern is known as "Apical Sparing" and is used to differentiate patients with cardiac amyloidosis from patients with other causes of left ventricular hypertrophy.

The reduced longitudinal strain in the basal lateral wall was found at the very early stages of Fabry disease in the absence of replacement fibrosis.

In patients with pulmonary arterial hypertension, conventional parameters of right ventricular systolic function may be normal despite abnormal right ventricular strain, which is an additional reason for the usage of this technique in these patients. Right ventricular longitudinal strain can identify subclinical dysfunction at the early phase of disease and may serve as an important marker of subtle right ventricular systolic dysfunction. Haeck et al. involved 150 pulmonary hypertension patients and demonstrated that right ventricular free-wall strain ≥-19%, unlike conventional parameters, was an independent predictor of all-cause mortality in these patients. Furthermore, change of right ventricular strain during therapy and follow-up is important for prognosis of these patients. Hardegree et al. reported that ≥5% improvement in right ventricular free-wall longitudinal strain had >7-fold lower mortality during the follow-up of 4 years.

Several studies have been conducted regarding the role of right ventricular strain in risk stratification of patients with tricuspid regurgitation. One of them included 896 patients with significant tricuspid regurgitation. Mortality was significantly higher in patients with decreased fractional area change, decreased Tricuspid Annular Plane Systolic Excursion, and impaired RV free wall longitudinal strain. However, after adjustment for concomitant diseases (diabetes mellitus, chronic kidney disease, coronary artery disease) as well as New York Heart Association class III/IV this independent predictive value vanished for other parameters, but not for RV free-wall strain.

The Role of Global Longitudinal Strain in Chronic Kidney Disease Patients

It is well known that chronic kidney disease accelerates the development of cardiovascular disease and increases mortality. The main reasons for cardiovascular death in advanced kidney disease are progressive heart failure and sudden cardiac death, which can be prevented by making early diagnosis. Speckle tracking echocardiography is available, easily utilizable and shows higher reproducibility than tissue Doppler imaging-derived strain modality. Several studies have been conducted in patients with chronic kidney disease using global longitudinal strain. In an attempt to identify subclinical left ventricular dysfunction in early-stage chronic kidney disease, Edwards et al. compared the longitudinal deformation indices of 40 CKD stage 2/3 patients (with no history of cardiovascular disease or diabetes mellitus) with 30 healthy controls. Once again, even though left ventricular ejection fraction was similar in the two groups, there was reduced global longitudinal strain among CKD patients.

The study conducted by Krishnasamy and colleagues investigated the prognostic value of global longitudinal strain over ejection fraction in patients with advanced chronic kidney disease. It included 183 patients with CKD stage 4, 5 and 5Dialysis. Impaired global longitudinal strain (>-16%) was associated with a 5.6-fold increased unadjusted risk of cardiovascular mortality in patients with preserved ejection fraction. Another interesting finding of the current study was that 51% of patients with normal ejection fraction had impaired strain.

Panoulas et al. tried to identify subclinical left ventricular myocardial dysfunction using speckle tracking echocardiography in patients with chronic kidney disease, preserved left ventricular ejection fraction, and no cardiovascular history or symptoms. They concluded that in patients with impaired global longitudinal strain, there was an increased rate of major adverse cardiovascular events during follow-up.

Sulemane et al. demonstrated a significant, independent relationship between impaired global longitudinal strain and major adverse cardiovascular events in CKD patients with no cardiovascular disease and normal ejection fraction. In their cohort a GLS of −17.7% or less had a good discriminative power (sensitive and specificity) to predict major adverse cardiovascular events. Another interesting finding of the current study was that, at baseline, patients that reached composite primary end-point had significantly impaired global longitudinal strain compared to patients who did not suffer major adverse cardiovascular events, even though left ventricular ejection fraction was similar in both groups. This fact suggests that global longitudinal strain may be able to detect CKD-related myocardial changes early in its course, as it primarily evaluates the function of subendocardial longitudinal fibres that are more sensitive to cardiac injury.

Conclusion

Chronic Kidney Disease and cardiovascular disease are closely linked, with CKD increasing the risk of cardiovascular complications such as heart failure and coronary artery disease. This relationship is driven by shared risk factors like hypertension, diabetes, and dyslipidemia. The concept of cardiorenal syndrome highlights the bidirectional nature of this interaction, where kidney dysfunction worsens heart disease and vice versa. Emerging cardiovascular-kidney-metabolic syndrome further underscores the role of metabolic disorders in accelerating both conditions. Speckle-tracking echocardiography, particularly global longitudinal strain, has proven valuable in detecting early myocardial dysfunction in CKD patients, offering

critical prognostic insights. Early detection of left ventricular abnormalities through global longitudinal strain can guide interventions to prevent progression to severe cardiovascular outcomes. Managing chronic kidney disease and cardiovascular disease together, with advanced diagnostic techniques, is essential for improving patient outcomes, highlighting the need for a multidisciplinary approach to address this complex health challenge.

Referencs

1. Jahn L, Kramann R, Marx N, Floege J, Becker M, Schlieper G. 'Speckle tracking echocardiography and all-cause and cardiovascular mortality risk in chronic kidney disease patients.' Kidney and Blood Pressure Research. 2019 Aug 15;44(4):690-703.
2. Evans M, Lewis RD, Morgan AR, Whyte MB, Hanif W, Bain SC, Davies S, Dashora U, Yousef Z, Patel DC, Strain WD. 'A narrative review of chronic kidney disease in clinical practice: current challenges and future perspectives.' Advances in therapy. 2022 Jan;39(1):33-43.
3. Jankowski J, Floege J, Fliser D, Böhm M, Marx N. 'Cardiovascular disease in chronic kidney disease: pathophysiological insights and therapeutic options.' Circulation. 2021 Mar 16;143(11):1157-72.
4. Mule G, Castiglia A, Cusumano C, Scaduto E, Geraci G, Altieri D, Di Natale E, Cacciatore O, Cerasola G, Cottone S. Subclinical kidney damage in hypertensive patients: a renal window opened on the cardiovascular system. Focus on microalbuminuria. Hypertension: from basic research to clinical practice. 2017:279-306.
5. Matsushita K, Kwak L, Ballew SH, Grams ME, Selvin E, Folsom AR, Coresh J, Tang W. 'Chronic kidney disease measures and the risk of abdominal aortic aneurysm.' Atherosclerosis. 2018 Dec 1;279:107-13.
6. Major RW, Cheng MR, Grant RA, Shantikumar S, Xu G, Oozeerally I, Brunskill NJ, Gray LJ. 'Cardiovascular disease risk factors in chronic kidney disease: A systematic review and meta-analysis.' PloS one. 2018 Mar 21;13 (3):e0192895.
7. Herzog CA, Asinger RW, Berger AK, Charytan DM, Díez J, Hart RG, Eckardt KU, Kasiske BL, McCullough PA, Passman RS, DeLoach SS. 'Cardiovascular disease in chronic kidney disease. A clinical update from Kidney Disease: Improving Global Outcomes (KDIGO).' Kidney international. 2011 Sep 2;80(6):572-86.33.
8. McCullough PA. 'Cardiovascular disease in chronic kidney disease from a cardiologist's perspective. 'Current opinion in nephrology and hypertension. 2004 Nov 1;13(6):591-600.
9. Cerasola G, Nardi E, Palermo A, Mulè G, Cottone S. 'Epidemiology and pathophysiology of left ventricular abnormalities in chronic kidney disease: a review.' mortality. 2011 Feb 2;12:15.
10. Schiffrin, E.L., Lipman, M.L. and Mann, J.F., 2007. 'Chronic kidney disease: effects on the cardiovascular system.' *Circulation*, *116*(1), pp.85-97.
11. Verma S, Graham MM, Lecamwasam A, Romanovsky A, Duggan S, Bagshaw S, Senaratne JM. 'Cardiorenal interactions: a review.' CJC open. 2022 Oct 1;4 (10):873-85.
12. Prastaro M, Nardi E, Paolillo S, Santoro C, Parlati AL, Gargiulo P, Basile C, Buonocore D, Esposito G, Filardi PP. 'Cardiorenal syndrome: Pathophysiology as a key to the therapeutic approach in an under-diagnosed disease.' Journal of Clinical Ultrasound. 2022 Oct;50(8):1110-24.
13. Lekawanvijit S. 'Cardiotoxicity of uremic toxins: a driver of cardiorenal syndrome.' Toxins. 2018 Sep 1;10(9):352.
14. Ndumele CE, Rangaswami J, Chow SL, Neeland IJ, Tuttle KR, Khan SS, Coresh J, Mathew RO, Baker-Smith CM, Carnethon MR, Despres JP. 'Cardiovascular-kidney-metabolic health: a presidential advisory from the American Heart Association.' Circulation. 2023 Nov 14;148(20):1606-35.
15. Bedo D, Beaudrey T, Florens N. 'Unraveling chronic cardiovascular and kidney disorder through the butterfly effect.' Diagnostics. 2024 Feb 20;14 (5):463.
16. Zoccali C, Mallamaci F, Halimi M, Rossignol P, Serafidis P, De Caterina R, Giugliano R, Zannad F. 'From Cardio Renal Syndrome to Chronic Cardiovascular and Kidney Disorder: A Conceptual Transition.' Clinical Journal of the American Society of Nephrology. 2023 Oct 30:10-2215.
17. Zannad F, Rossignol P. 'Cardiorenal syndrome revisited.' Circulation. 2018 Aug 28;138(9):929-44.
18. Pliquett RU. 'Cardiorenal syndrome: an updated classification based on clinical hallmarks.' Journal of Clinical Medicine. 2022 May 20;11(10):2896.
19. Patel RB, Ter Maaten JM, Ferreira JP, McCausland FR, Shah SJ, Rossignol P, Solomon SD, Vaduganathan M, Packer M, Thompson A, Stockbridge N. 'Challenges of cardio-kidney composite outcomes in large-scale clinical trials.' Circulation. 2021 Mar 2;143(9):949-58.
20. Paoletti E, De Nicola L, Gabbai FB, Chiodini P, Ravera M, Pieracci L, Marre S, Cassottana P, Lucà S, Vettoretti S, Borrelli S. 'Associations of left ventricular hypertrophy and geometry with adverse outcomes in patients with CKD and hypertension.' Clinical journal of the American Society of Nephrology. 2016 Feb 1;11(2):271-9.
21. Cai QZ, Lu XZ, Lu Y, Wang AY. 'Longitudinal changes of cardiac structure and function in CKD (CASCADE study).' Journal of the American Society of Nephrology. 2014 Jul 1;25(7):1599-608.
22. Hassanin N, Alkemary A. 'Early detection of subclinical uremic cardiomyopathy using two-dimensional speckle tracking echocardiography.' Echocardiography. 2016 Apr;33(4):527-36.
23. Jain A, Scott C, Chen HH. 'The renal–cardiac connection in subjects with preserved ejection fraction: a population based study.' ESC Heart Failure. 2017 Aug;4(3):266-73.
24. Gan GC, Kadappu KK, Bhat A, Fernandez F, Eshoo S, Thomas L. 'Exercise E/e' is a determinant of exercise capacity and adverse cardiovascular outcomes in chronic kidney disease.' Cardiovascular Imaging. 2020 Dec 1;13 (12):2485-94.
25. Holland DJ, Prasad SB, Marwick TH. 'Contribution of exercise echocardiography to the diagnosis of heart failure with preserved ejection fraction (HFpEF).' Heart. 2010 Jul 1;96(13):1024-8.
26. 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 nephrology. 2013 Dec;14:1-6.
27. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, Marino P. '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.' European Journal of Echocardiography. 2016 Jul 15;17(12):1321-60.
28. Obokata M, Kane GC, Reddy YN, Olson TP, Melenovsky V, Borlaug BA. 'Role of diastolic stress testing in the evaluation for heart failure with preserved ejection fraction: a simultaneous invasive-echocardiographic study.' Circulation. 2017 Feb 28;135(9):825-38.
29. Kosmala W, Przewlocka-Kosmala M, Rojek A, Marwick TH. 'Comparison of the diastolic stress test with a combined resting echocardiography and biomarker approach to patients with exertional dyspnea: diagnostic and prognostic implications.' JACC: Cardiovascular Imaging. 2019 May;12(5):771-80.
30. Samad Z, Sivak JA, Phelan M, Schulte PJ, Patel U, Velazquez EJ. 'Prevalence and outcomes of left-sided valvular heart disease associated with chronic kidney disease.' Journal of the American Heart Association. 2017 Oct 11;6 (10):e006044.
31. Krishnasamy R, Isbel NM, Hawley CM, Pascoe EM, Leano R, Haluska BA, Stanton T. 'The association between left ventricular global longitudinal strain, renal impairment and all-cause mortality.' Nephrology Dialysis Transplantation. 2014 Jun 1;29(6):1218-25.
32. Buckberg G, Hoffman JI, Mahajan A, Saleh S, Coghlan C. 'Cardiac mechanics revisited: the relationship of cardiac architecture to ventricular function.' Circulation. 2008 Dec 9;118(24):2571-87.
33. Hayashi K, Suzuki T, Sakamaki Y, Ito S. 'Cardiac hypertrophy in chronic kidney disease—role of Aldosterone and FGF23.' Renal Replacement Therapy. 2018 Dec;4:1-2.
34. Chillo P, Mujuni E. 'Prevalence and predictors of left ventricular dysfunction among patients with chronic kidney disease attending Muhimbili National Hospital in Tanzania—a cross-sectional study.' Research Reports in Clinical Cardiology. 2018 May 21:11-21.
35. Halliday BP, Senior R, Pennell DJ. 'Assessing left ventricular systolic function: from ejection fraction to strain analysis.' European Heart Journal. 2021 Feb 14;42(7):789-97.
36. Verdonschot JA, Merken JJ, Brunner-La Rocca HP, Hazebroek MR, Eurlings CG, Thijssen E, Wang P, Weerts J, van Empel V, Schummers G, Schreckenberg M. 'Value of speckle tracking–based deformation analysis in screening relatives of patients with asymptomatic dilated cardiomyopathy.' Cardiovascular Imaging. 2020 Feb 1;13(2_Part_2):549-58.
37. Amzulescu MS, De Craene M, Langet H, Pasquet A, Vancraeynest D, Pouleur AC, Vanoverschelde JL, Gerber BL. 'Myocardial strain imaging: review of general principles, validation, and sources of discrepancies.' European Heart Journal-Cardiovascular Imaging. 2019 Jun 1;20(6):605-19.
38. Pieske B, Tschöpe C, De Boer RA, Fraser AG, Anker SD, Donal E, Edelmann F, Fu M, Guazzi M, Lam CS, Lancellotti P. 'How to diagnose heart failure with preserved ejection fraction: the HFA–PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC).' European heart journal. 2019 Oct 21;40(40):3297-317.
39. Ernande L, Audureau E, Jellis CL, Bergerot C, Henegar C, Sawaki D, Czibik G, Volpi C, Canoui-Poitrine F, Thibault H, Ternacle J. 'Clinical implications of echocardiographic phenotypes of patients with diabetes mellitus.' Journal of the American College of Cardiology. 2017 Oct 3;70(14):1704-16.
40. Holland DJ, Marwick TH, Haluska BA, Leano R, Hordern MD, Hare JL, Fang ZY, Prins JB, Stanton T. 'Subclinical LV dysfunction and 10-year outcomes in type 2 diabetes mellitus.' Heart. 2015 Jul 1;101(13):1061-6.
41. Lee WH, Liu YW, Yang LT, Tsai WC. 'Prognostic value of longitudinal strain of subepicardial myocardium in patients with hypertension.' Journal of Hy-

pertension. 2016 Jun 1;34(6):1195-200.
42. Park JJ, Park JB, Park JH, Cho GY. 'Global longitudinal strain to predict mortality in patients with acute heart failure.' Journal of the American College of Cardiology. 2018 May 8;71(18):1947-57.
43. Kalam K, Otahal P, Marwick TH. 'Prognostic implications of global LV dysfunction: a systematic review and meta-analysis of global longitudinal strain and ejection fraction.' Heart. 2014 Nov 1;100(21):1673-80.
44. Ishizu T, Seo Y, Kameda Y, Kawamura R, Kimura T, Shimojo N, Xu D, Murakoshi N, Aonuma K. 'Left ventricular strain and transmural distribution of structural remodeling in hypertensive heart disease.' Hypertension. 2014 Mar;63(3):500-6.
45. Lancellotti P, Magne J, Dulgheru R, Clavel MA, Donal E, Vannan MA, Chambers J, Rosenhek R, Habib G, Lloyd G, Nistri S. 'Outcomes of patients with asymptomatic aortic stenosis followed up in heart valve clinics.' JAMA cardiology. 2018 Nov 1;3(11):1060-8.
46. Magne J, Cosyns B, Popescu BA, Carstensen HG, Dahl J, Desai MY, Kearney L, Lancellotti P, Marwick TH, Sato K, Takeuchi M. 'Distribution and prognostic significance of left ventricular global longitudinal strain in asymptomatic significant aortic stenosis: an individual participant data meta-analysis.' JACC: Cardiovascular Imaging. 2019 Jan;12(1):84-92.
47. Tanaka H. 'Efficacy of echocardiography for differential diagnosis of left ventricular hypertrophy: special focus on speckle-tracking longitudinal strain.' Journal of echocardiography. 2021 Jun;19(2):71-9.
48. Soufi Taleb Bendiab N, Meziane-Tani A, Ouabdesselam S, Methia N, Latreche S, Henaoui L, Monsuez JJ, Benkhedda S. 'Factors associated with global longitudinal strain decline in hypertensive patients with normal left ventricular ejection fraction.' European journal of preventive cardiology. 2017 Sep 1;24 (14):1463-72.
49. Barros-Gomes S, Williams B, Nhola LF, Grogan M, Maalouf JF, Dispenzieri A, Pellikka PA, Villarraga HR. 'Prognosis of light chain amyloidosis with preserved LVEF: added value of 2D speckle-tracking echocardiography to the current prognostic staging system.' JACC: Cardiovascular Imaging. 2017 Apr;10(4):398-407.
50. Phelan D, Collier P, Thavendiranathan P, Popović ZB, Hanna M, Plana JC, Marwick TH, Thomas JD. 'Relative apical sparing of longitudinal strain using two-dimensional speckle-tracking echocardiography is both sensitive and specific for the diagnosis of cardiac amyloidosis.' Heart. 2012 Oct 1;98 (19):1442-8.
51. Krämer J, Niemann M, Liu D, Hu K, Machann W, Beer M, Wanner C, Ertl G, Weidemann F. 'Two-dimensional speckle tracking as a non-invasive tool for identification of myocardial fibrosis in Fabry disease.' European Heart Journal. 2013 Jun 1;34(21):1587-96.
52. Tadic M, Nita N, Schneider L, Kersten J, Buckert D, Gonska B, Scharnbeck D, Reichart C, Belyavskiy E, Cuspidi C, Rottbauer W. 'The predictive value of right ventricular longitudinal strain in pulmonary hypertension, heart failure, and valvular diseases.' Frontiers in Cardiovascular Medicine. 2021 Jun 17;8:698158.
53. Badano LP, Muraru D, Parati G, Haugaa K, Voigt JU. 'How to do right ventricular strain.' European Heart Journal-Cardiovascular Imaging. 2020 Aug 1;21(8):825-7.
54. Ancona F, Melillo F, Calvo F, Attalla El Halabieh N, Stella S, Capogrosso C, Ingallina G, Tafciu E, Pascaretta A, Ancona MB, De Bonis M. 'Right ventricular systolic function in severe tricuspid regurgitation: prognostic relevance of longitudinal strain.' European Heart Journal-Cardiovascular Imaging. 2021 Aug 1;22(8):868-75.
55. van Kessel M, Seaton D, Chan J, Yamada A, Kermeen F, Butler T, Sabapathy S, Morris N. 'Prognostic value of right ventricular free wall strain in pulmonary hypertension patients with pseudo-normalized tricuspid annular plane systolic excursion values.' The international journal of cardiovascular imaging. 2016 Jun;32:905-12.
56. Hardegree EL, Sachdev A, Villarraga HR, Frantz RP, McGoon MD, Kushwaha SS, Hsiao JF, McCully RB, Oh JK, Pellikka PA, Kane GC. 'Role of serial quantitative assessment of right ventricular function by strain in pulmonary arterial hypertension.' The American journal of cardiology. 2013 Jan 1;111(1):143-8.
57. Prihadi EA, van der Bijl P, Dietz M, Abou R, Vollema EM, Marsan NA, Delgado V, Bax JJ. 'Prognostic implications of right ventricular free wall longitudinal strain in patients with significant functional tricuspid regurgitation.' Circulation: Cardiovascular Imaging. 2019 Mar;12(3):e008666.
58. Bannehr M, Kahn U, Liebchen J, Okamoto M, Haehnel V, Georgi C, Dworok V, Edlinger C, Lichtenauer M, Kuecken T, Kropf S. 'Right ventricular longitudinal strain predicts survival in patients with functional tricuspid regurgitation.' Canadian Journal of Cardiology. 2021 Jul 1;37(7):1086-93.
59. Hensen LC, Goossens K, Delgado V, Rotmans JI, Jukema JW, Bax JJ. 'Prognostic implications of left ventricular global longitudinal strain in predialysis and dialysis patients.' The American Journal of Cardiology. 2017 Aug 1;120(3):500-4.
60. Alhaj E, Alhaj N, Rahman I, Niazi TO, Berkowitz R, Klapholz M. 'Uremic cardiomyopathy: an underdiagnosed disease.' Congestive heart failure. 2013 Jul;19(4):E40-5. 26. Evans, M.
61. Evans M, Lewis RD, Morgan AR, Whyte MB, Hanif W, Bain SC, Davies S, Dashora U, Yousef Z, Patel DC, Strain WD. 'A narrative review of chronic kidney disease in clinical practice: current challenges and future perspectives.' Advances in therapy. 2022 Jan;39(1):33-43.
62. Jankowski J, Floege J, Fliser D, Böhm M, Marx N. 'Cardiovascular disease in chronic kidney disease: pathophysiological insights and therapeutic options.' Circulation. 2021 Mar 16;143(11):1157-72.
63. Mule G, Castiglia A, Cusumano C, Scaduto E, Geraci G, Altieri D, Di Natale E, Cacciatore O, Cerasola G, Cottone S. 'Subclinical kidney damage in hypertensive patients: a renal window opened on the cardiovascular system. Focus on microalbuminuria.' Hypertension: from basic research to clinical practice. 2017:279-306.
64. Matsushita K, Kwak L, Ballew SH, Grams ME, Selvin E, Folsom AR, Coresh J, Tang W. 'Chronic kidney disease measures and the risk of abdominal aortic aneurysm.' Atherosclerosis. 2018 Dec 1;279:107-13.
65. Major RW, Cheng MR, Grant RA, Shantikumar S, Xu G, Oozeerally I, Brunskill NJ, Gray LJ. 'Cardiovascular disease risk factors in chronic kidney disease: A systematic review and meta-analysis.' PloS one. 2018 Mar 21;13 (3):e0192895.
66. Herzog CA, Asinger RW, Berger AK, Charytan DM, Díez J, Hart RG, Eckardt KU, Kasiske BL, McCullough PA, Passman RS, DeLoach SS. 'Cardiovascular disease in chronic kidney disease. A clinical update from Kidney Disease: Improving Global Outcomes (KDIGO).' Kidney international. 2011 Sep 2;80(6):572-86.
67. 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?' Journal of the American Society of Echocardiography. 2008 Dec 1;21(12):1293-8.
68. Krishnasamy R, Isbel NM, Hawley CM, Pascoe EM, Burrage M, Leano R, Haluska BA, Marwick TH, Stanton T. 'Left ventricular global longitudinal strain (GLS) is a superior predictor of all-cause and cardiovascular mortality when compared to ejection fraction in advanced chronic kidney disease.' PLoS One. 2015 May 15;10(5):e0127044.
69. Panoulas VF, Sulemane S, Konstantinou K, Bratsas A, Elliott SJ, Dawson D, Frankel AH, Nihoyannopoulos P. Early detection of subclinical left ventricular myocardial dysfunction in patients with chronic kidney disease. European Heart Journal-Cardiovascular Imaging. 2015 May 1;16(5):539-48.
70. Sulemane S, Panoulas VF, Bratsas A, Grapsa J, Brown EA, Nihoyannopoulos P. 'Subclinical markers of cardiovascular disease predict adverse outcomes in chronic kidney disease patients with normal left ventricular ejection fraction.' The international journal of cardiovascular imaging. 2017 May;33:687-98.
71. Park JH, Marwick TH. 'Use and limitations of E/e' to assess left ventricular filling pressure by echocardiography.' Journal of cardiovascular ultrasound. 2011 Dec 1;19(4):169-73.
72. Kim MK, Kim B, Lee JY, Kim JS, Han BG, Choi SO, Yang JW. 'Tissue Doppler-derived E/e'ratio as a parameter for assessing diastolic heart failure and as a predictor of mortality in patients with chronic kidney disease.' The Korean journal of internal medicine. 2012 Dec 28;28(1):35.
73. Buckberg G, Hoffman JI, Mahajan A, Saleh S, Coghlan C. 'Cardiac mechanics revisited: the relationship of cardiac architecture to ventricular function.' Circulation. 2008 Dec 9;118(24):2571-87.
74. Iwama K, Nakanishi K, Daimon M, Yoshida Y, Sawada N, Hirose K, Yamamoto Y, Ishiwata J, Hirokawa M, Kaneko H, Nakao T. 'Chronic kidney disease and subclinical abnormalities of left heart mechanics in the community.' European Heart Journal Open. 2021 Nov 1;1(3):oeab037.
75. Yoshida Y, Nakanishi K, Daimon M, Ishiwata J, Sawada N, Hirokawa M, Kaneko H, Nakao T, Mizuno Y, Morita H, Di Tullio MR. 'Alteration of cardiac performance and serum B-type natriuretic peptide level in healthy aging.' Journal of the American College of Cardiology. 2019 Oct 8;74 (14):1789-800.
76. Negishi K, Negishi T, Haluska BA, Hare JL, Plana JC, Marwick TH. 'Use of speckle strain to assess left ventricular responses to cardiotoxic chemotherapy and cardioprotection.' European Heart Journal–Cardiovascular Imaging. 2014 Mar 1;15(3):324-31.
77. Venkateshvaran A, Sarajlic P, Lund LH, Friden C, Nordgren B, Opava CH, Lundberg IE, Larsson SC, Manouras A, Bäck M. 'Impaired left atrial dynamics and its improvement by guided physical activity reveal left atrial strain as a novel early indicator of reversible cardiac dysfunction in rheumatoid arthritis.' European Journal of Preventive Cardiology. 2018 Jul;25(10):1106-8.
78. Lobzhanidze G. 'The role of right-sided heart failure in patients with Cardio-Renal Syndrome.' Translational and Clinical Medicine-Georgian Medical Journal. 2016 Dec 12;1(2):15-8.