

# Multi-modality cardiac imaging in advanced chronic kidney disease

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## Abstract

Cardiovascular disease (CVD) is the leading cause of death worldwide and is particularly frequent among those with severe renal impairment. Early diagnosis and therapeutic intervention may help alleviate the burden of cardiovascular complication within this population. In the last years, advances have been made toward developing noninvasive imaging techniques that could offer better insight into the cardiac involvement in end-stage renal disease (ESRD). Conventional transthoracic echocardiography remains the first-line investigation used to assess cardiac function, but encompassing in our daily practice, the newer approaches such as speckle-tracking imaging, cardiac computed tomography, or cardiac magnetic resonance can guide us to a more comprehensive understanding of CVD in ESRD. Given that patients with chronic kidney disease may not present with typical CVD symptoms, the amount of information brought by newer imaging techniques is crucial for an accurate diagnosis, risk stratification, and further management. The purpose of this review is to briefly summarize the specific applications of standard cardiac imaging techniques in patients with ESRD and to offer insight into the novel imaging modalities, highlighting the newest research in this field. By doing so, we aim to identify the most important imaging predictors of clinical outcomes in this population.

## KEYWORDS

cardiac magnetic resonance, echocardiography, ESRD, MDCT, speckle-tracking echocardiography

## 1 | INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of death worldwide, causing more than 17.9 million deaths in 2016.<sup>1</sup> Chronic kidney disease (CKD) doubles the risk of CVD, worsening its prognosis, both short- and long-term. Among patients with renal impairment, death from CVD is six times more frequent than progression to end-stage renal disease (ESRD).<sup>2</sup> Furthermore, studies report that more than 80% of the individuals with ESRD have CVD.<sup>3</sup> In fact,

echocardiographic abnormalities are almost universal,<sup>4</sup> with a recent study in 315 patients with ESRD showing that only 11.5% and 3.4% of all patients had normal left ventricular (LV) geometry and normal LV filling pattern, respectively.<sup>5</sup>

Nevertheless, the field of cardiovascular imaging has evolved significantly during the past decade, with advances in echocardiography techniques and improvements in newer imaging modalities, such as cardiac computed tomography (CT) and magnetic resonance (CMR). Given that patients with CKD may either present with

dyspnea secondary to volume overload in the absence of CVD, or on the contrary may not develop classical symptoms, the amount of information brought by newer imaging techniques is crucial for an accurate diagnosis and management.<sup>6</sup>

The purpose of this review is to briefly summarize the specific applications of standard cardiac imaging techniques in patients with ESRD and to offer insight into the novel imaging modalities, highlighting the newest research in this field. By doing so, we aim to identify the most important imaging predictors of clinical outcomes in this population.

## 2 | CONVENTIONAL TRANSTHORACIC ECHOCARDIOGRAPHY (TTE)

Transthoracic echocardiography is one of the most useful diagnostic tools, and given its multiple clinical applications, it has remained the first-line investigation for suspected cardiac disease.

Dyspnea and signs of congestion are central for the diagnosis of heart failure. In patients with ESRD and especially in case of dialysis, distinguishing between heart failure and volume overload secondary to renal impairment can be particularly challenging. Therefore, in order to facilitate an accurate diagnosis, the Acute Dialysis Quality Initiative (ADQI) XI Workgroup designed a system that includes eight essential parameters reflecting structural abnormalities: LV hypertrophy, increased LV volume index, LV ejection fraction of 45% or less, regional wall-motion abnormalities, diastolic dysfunction, left atrial enlargement, mitral or aortic valvular disease, right ventricular systolic dysfunction. This system defines heart failure in dialysis by the presence of at least one echocardiographic criterion, dyspnea and the remission of it by dialysis or ultrafiltration.<sup>7</sup>

Apart from diagnosing certain cardiac diseases, TTE is useful for stratifying risk and evaluating the impact of certain interventions, such as dialysis or renal transplantation (RTx).<sup>8</sup> Table 1. summarizes the best validated TTE parameters in ESRD.

### 2.1 | Left ventricular hypertrophy (LVH)

Important data from the Chronic Renal Insufficiency Cohort (CRIC) study group regarding the association between kidney function and subclinical cardiac abnormalities, showed that LVH is the main myocardial alteration in CKD, with a multifactorial etiology, including the recently ascribed major role of FGF23, alongside volume overload and increased afterload from higher BP and/or arterial stiffness. Patients with an eGFR < 30 mL/min have a twofold higher risk of LVH, and LV mass correlates directly to eGFR, independently of brain natriuretic peptide (BNP)—as a biomarker of volume overload.<sup>9</sup> In ESRD, uremia-related cardiomyopathy is characterized by myocardial fibrosis and LVH. Furthermore, the prevalence of LVH (either concentric or eccentric) reaches an impressive proportion of up to 74%, as reported by Foley et al, and is associated (particularly the eccentric subtype) with a much higher medium-term CV and

**TABLE 1** Validated transthoracic echocardiography (TTE) parameters in end-stage renal disease

TTE parameter	Correlation
LVH	MACE <sup>9</sup>
LV mass	Renal deaths <sup>9</sup> eGFR <sup>10</sup>
LV ejection fraction	All-cause and CV mortality <sup>15,16</sup> Worsening renal function <sup>94</sup>
Diastolic dysfunction (E/e', LAVi)	All-cause and CV mortality <sup>5,18,20,22-25</sup>
RV dysfunction	All-cause mortality <sup>30</sup>
Pulmonary hypertension	CV mortality and events HF hospitalization <sup>36,37</sup>
Valvular calcifications	Coronary artery disease <sup>42</sup>
Global longitudinal strain	All-cause and CV mortality MACE HF hospitalization <sup>48-51,53</sup>

renal risk.<sup>10</sup> RTx can lead to regression of hypertrophy in concentric LVH.<sup>11-14</sup>

### 2.2 | Systolic function—left ventricular ejection fraction (LVEF)

One of the most powerful predictors of death and CV morbidity, the LVEF—as determined by 2D conventional TTE, is traditionally used to assess systolic function. Studies have proven its independent correlation with all-cause and cardiovascular mortality in ESRD/dialysis patients.<sup>15,16</sup> The issue of using LVEF in ESRD arises mainly from its dependency on loading conditions which can affect its accuracy, especially in patients undergoing dialysis, by emulating the typical clinical presentation of heart failure. Also, if the prognostic value of a low LVEF is well established, an LVEF > 45% is unable to grade risk.<sup>17</sup> RTx can alleviate systolic dysfunction, improve LV contractility and functional status of congestive heart failure.<sup>11,14</sup>

### 2.3 | Diastolic dysfunction (DD)

As CKD progresses, myocardial fibrosis leads to LV stiffness, causing impaired relaxation, high filling pressures, and DD. Studies showed that DD is present in 85%–100% of dialysis patients and at least 35% have grade 2 or higher dysfunction. Also, DD is an independent predictor of mortality for these patients.<sup>5,18</sup>

Worsening eGFR correlates with the degree of DD as assessed by the E/e' ratio.<sup>19</sup> E/e' ratio together with LV global longitudinal strain (LV GLS) is the most powerful echocardiographic predictors of CV events and mortality in dialysis patients.<sup>20</sup> An E/e' ratio > 15 is commonly used to identify high LV filling pressures. Peak E wave velocity correlates with the degree of volume overload and fluctuates with dialysis and ultrafiltration. In contrast, e' velocity reflects LV stiffness, independent of the patient's volume status.<sup>21</sup> This is particularly important since heart failure with preserved EF is the most prevalent form in ESRD, and diagnosing diastolic dysfunction by

accurately measuring  $E/e'$  ratio may facilitate early therapeutic intervention. In addition, given the high prevalence of valvular calcification in ESRD, it is important to remember that moderate-to-severe mitral annular calcification can affect the accuracy of  $e'$  measurement, when assessing DD. For such particular situations, the  $E/A$  ratio and isovolumic relaxation time can be useful predictors.<sup>22</sup>

Left atrial volume index (LAVi) is a well-validated indicator of DD in the general population. In ESRD, it is associated with plasma BNP and ANP levels and can help identify the patients at risk for myocardial ischemia.<sup>23,24</sup> LAVi is an independent predictor of death, and monitoring it by echocardiography can predict the risk of CV events in dialysis patients.<sup>25</sup>

The impact of RTx on DD is not entirely understood, as studies have reported conflicting results. Most data point toward the persistence of DD after RTx, despite the alleviation of LVH (see above), attributing this unexpected finding to immunosuppressant drugs, hypertension, and pre-RTx myocardial fibrosis.<sup>26-29</sup>

## 2.4 | Right ventricular (RV) dysfunction

Both RV systolic and diastolic dysfunction, measured by TAPSE,  $S'$ , and fractional area change, are common in ESRD patients on hemodialysis (HD) and are important predictors of mortality.<sup>30,31</sup> The pathophysiology of the RV involvement in ESRD is influenced by various factors such as chronic volume overload, anemia, hyperparathyroidism, and especially the presence of an brachial arteriovenous fistula (AVF). Once created, the AVF causes chronic RV overload, shifting the interventricular septum to the left and impairing LV filling and systolic function. This right-to-left ventricular interdependence is important in dialysis, as mortality is twofold higher in patients with biventricular dysfunction.<sup>32,33</sup>

## 2.5 | Pulmonary hypertension (PH)

Multiple studies have demonstrated a relationship between ESRD and the presence of PH<sup>34-37</sup> and showed that pulmonary artery systolic pressure (PASP) is associated with mortality and CV events, independently of BNP and EF. 40% of the dialysis patients are reported to have PH.<sup>35</sup> Several mechanisms have been postulated: PH may be a consequence of left-sided heart failure, of volume overload, or of the AVF which can influence PASP by affecting pulmonary vascular resistance and cardiac output.<sup>34</sup> A recent meta-analysis of 16 studies concluded that in ESRD, there is a twofold higher risk of HF admission and mortality compared to non-ESRD patients, both in HD and peritoneal dialysis, partially explained by a higher burden of PH in this population.<sup>37</sup>

## 2.6 | Valvular calcification

In HD patients, both vascular and valvular calcification are frequent, probably due to CKD-MBD derangements, inflammation, and cardiac overload.<sup>5,38-41</sup> In predialysis CKD, the presence of valvular calcification correlates with the presence and severity of coronary

artery disease, as shown by Kim YI et al., suggesting that assessment of cardiac calcification by TTE could be a valuable risk-stratification tool for CAD in these patients.<sup>42</sup> In stable HD patients, valvular calcifications are associated with worse systolic and diastolic function, more severe LVH, and poorer prognostic.<sup>43</sup>

## 3 | SPECKLE-TRACKING ECHOCARDIOGRAPHY (STE)

Left ventricular global longitudinal strain (GLS) is a marker of systolic function that was shown to be superior to LVEF for prediction of major adverse cardiac events in the general population.<sup>44</sup> GLS is increasingly reported to be a powerful prognostic tool as it is able to detect patients with overt systolic dysfunction in the presence of preserved LVEF.<sup>45</sup>

In uremic patients, impaired GLS could be due to microvascular ischemia, interstitial fibrosis, and myocyte hypertrophy caused by hypertension, uremic toxins, and HD-related myocardial stunning that affects the function of subendocardial longitudinal fibers.<sup>46,47</sup>

Global longitudinal strain was shown to have superior prognostic significance over LVEF in patients with renal impairment. Also, both classical Framingham risk factors and renal-specific disturbances, such as hyperphosphatemia, are significant determinants of GLS.<sup>48</sup> In a study by Hensen LCR et al,<sup>49</sup> patients in predialysis and dialysis were divided into four groups according to quartiles of LV GLS. The lowest quartile of GLS showed the worst prognosis and had a twofold increased risk of all-cause mortality after correcting for RTx.

Heart failure with preserved EF is the most frequent form of heart failure among ESRD patients.<sup>50</sup> As discussed above, cardiac remodeling in ESRD can lead to subclinical myocardial impairment despite maintaining EF in a (supra-) normal range. For this population, LV GLS is able to reveal the underlying myocardial damage and perhaps allow early therapeutic intervention since a reduced GLS < 15.2% is associated with increased HF hospitalizations and all-cause mortality.<sup>49,51</sup> No study has evaluated so far the impact of early implementation of HF treatment on CV outcomes based on LV GLS.

Reduced GLS peri-RTx is associated with the rate of hospitalization for CVD and all-cause mortality.<sup>52</sup> Additional studies are needed, as GLS could possibly be an useful tool for CV risk stratification pre-RTx. As for the impact of RTx on GLS, Hamidi et al<sup>28</sup> recently showed a favorable impact, with both subtle and gross changes in myocardial function improving after surgery.

Another possible role of STE in advanced CKD has recently been postulated, with a hypothesis-generating study showing that LV GLS and LV mechanical dispersion could identify the patients at risk for sudden cardiac death (SCD) due to mixture of scar and fibrous tissue within layers of viable myocardium, despite of relatively preserved LVEF.<sup>53</sup> Both autopsy and CMR studies showed that LV GLS correlated well with increased extend of myocardial fibrosis.<sup>54,55</sup> LV mechanical dispersion, as an indicator for the temporal heterogeneity of the mechanical LV contraction (secondary to the presence of myocardial

fibrosis), has been validated as a good predictor of SCD in several populations.<sup>56</sup> Myocardial fibrosis, which can interfere with the intracellular coupling, delay conduction, and increase the propensity to develop ventricular arrhythmias, is promoted in ESRD by ischemia, uremic toxins, and CKD-MBD derangements.<sup>57</sup> Further studies are needed in order to investigate the possible role of STE for detecting myocardial fibrosis and stratification of SCD risk for patients in ESRD.

Apart from LV GLS, RV GLS has recently proven specific enough to select the asymptomatic HD patients with subclinical dysfunction and normal RV fractional area change.<sup>31</sup>

#### 4 | REAL TIME 3D ECHOCARDIOGRAPHY (RT3DE)

Real time 3D echocardiography has emerged as a technique capable of better assessment of ventricular volumes and function when compared to conventional TTE, with results as accurate as the “gold-standard” method, CMR.<sup>58</sup> Apart from the indications validated for the general population, data regarding the specific use of RT3DE in ESRD are mostly confined to data obtained during dialysis sessions.

Intra-dialytic hypotension (IDH), although common, is still not completely understood, and assessing cardiac dynamics during HD seems a promising option. Conventional TTE can be performed, but geometric assumptions and volume miscalculations are frequent. CMR can overcome these limitations but cannot be performed during HD. Therefore, two studies addressed the issue of IDH by assessing LV function through RT3DE. First, in a pilot study on 12 patients, Krenning et al<sup>59</sup> proved the feasibility for accurate measuring of LV function through RT3DE, by assessing LV volumes and geometry during HD. Then, Ning-I Yang et al performed RT3DE in 29 dialysis patients with IDH and 34 controls and showed that patients with IDH had greater decrease in 3DLVEF, stroke volume, and cardiac index at mid-dialysis, with 3DLVEF being the strongest predictor independently associated with IDH. Moreover, the study proved that the presence of IDH was not associated with a reflex increase in heart rate, probably secondary to autonomic dysfunction.<sup>60</sup>

The role of the RV in the development of IDH was recently assessed by Sun et al,<sup>61</sup> showing that RVEF as assessed by 3DSTE is associated with an increased risk of IDH and may serve for risk stratification in HD patients, whereas lower ultrafiltration rates could be protective for the RV. Another small study used 3DSTE in order to assess the impact of HD on LV mechanics and proved that HD sessions immediately improve all strain directions and pointed toward FGF23 as playing a role in the deterioration of LV mechanics in patients with ESRD.<sup>62</sup>

Precisely measuring LV volumes in response to blood volume changes is another promising application of RT3DE, as it was shown that in HD patients with DD, colloid infusion determines a decrease in stroke volume variability (SVV), but no change in LV EDV. This finding suggests that HD patients are responsive to fluid infusion and SVV can represent a tool in intra-operative guiding of fluid therapy.<sup>63</sup>

#### 5 | CARDIAC COMPUTED TOMOGRAPHY

Chronic kidney disease is an independent risk factor for developing coronary artery disease (CAD), and its presence in ESRD is associated with a threefold higher risk of death. In dialysis, both atherosclerotic plaques and coronary artery calcifications (CAC) can lead to significant coronary artery stenosis.<sup>41</sup> The pathophysiology of developing CAD in ESRD involves a series of traditional risk factors such as age, hypertension, diabetes mellitus, dyslipidemia, and specific CKD-related factors such as hyperparathyroidism, hyperphosphatemia, endothelial dysfunction, chronic inflammation, and the presence of epicardial adipose tissue.<sup>64</sup>

Coronary atherosclerosis encompasses the vast majority of the CAD spectrum for the general population. However, in CKD, CAC are more frequent, severe, rapidly progressive and associated with mortality, a poorer CV outcome, and worse CKD-MBD derangements. In the general population, CAC reflect subintimal atherosclerosis, whereas in CKD, CAC correlate with calcium and phosphorus deposits in the media layer of the arterial wall.<sup>65</sup> RTx significantly reduces CAC score in dialysis patients by interference with the calcium-phosphorus homeostasis.<sup>66</sup>

Given its high prevalence, efforts have been made toward developing noninvasive techniques for assessing CAD in this population. Single photon emission computed tomography (SPECT) and electron beam computed tomography (EBCT) showed promising results, but failed to enter clinical practice for individuals with ESRD due to low sensitivity, spatial resolution, and high pricing.<sup>67</sup>

Multi-detector computed tomography (MDCT) is currently available in many units and allows physicians to screen for coronary lesions in a noninvasive way. In order to obtain high-quality information, the patient's heart rate must be below 65 bpm. Then, according to the American Heart Association model of the coronary tree, every artery is analyzed by segment and diameter and the degree of coronary stenosis is assessed—a significant lesion is defined as a luminal narrowing of 50% or more.<sup>67</sup> Iio et al<sup>68</sup> were the first group to report good sensitivity, specificity, positive and negative predictive value for MDCT in detecting significant coronary artery stenosis when compared to coronary angiography. In asymptomatic ESRD patients, coronary artery stenosis is highly prevalent, and therefore early diagnosis through MDCT could help select those who would benefit from a more invasive approach.

Also, based on the MDCT, the Agatston score can be quantified by an automatic CAC scoring software; this score can serve as a marker of CAD, as it correlates well with significant coronary artery stenosis as assessed by invasive coronary angiography.<sup>69</sup> Patients with both atherosclerotic plaques and calcification are at higher risk for CV events, and thus, MDCT plays an important role in diagnosing both entities.<sup>67</sup>

For the general population, there are several risk score calculators that include CAC score as a variable, such as MESA or arterial age calculator. MESA risk score calculator was developed by the investigators of the MESA study by adding CAC score to traditional risk factors for CVD. The modified variant including CAC proved to be superior as far as risk prediction (C-statistic 0.80 vs 0.75,

$P < 0.0001$ ), providing an accurate estimate of 10-year CAD risk.<sup>70</sup> In spite of CKD and ESRD patients having a higher burden of vascular calcification, none of the risk score calculators take into account renal function as a variable and there are no studies validating their use in advanced CKD.

There are certain limitations of MDCT use in ESRD. First of all, the presence of high-degree vascular calcifications can lead to misinterpretation of results as it is difficult to differentiate high-contrast calcium from contrast-enhanced vessel lumen. Secondly, MDCT cannot separate medial from intimal (atherosclerotic) calcifications. Furthermore, the requirement of iodinated contrast agents can alter the residual renal function (RRF) in patients on RRT. This is important, given the benefits of RRF such as reducing inflammation, improving fluid management, and providing continuous clearance of protein-bound solutes and middle molecules. RRF is associated with improved survival and quality of life in dialysis patients and preserving it is imperative. Therefore, using iodinated contrast agents in patients on dialysis is not risk-free and careful monitoring of fluid status and serum potassium are required. Immediate or supplementary HD is not usually necessary.<sup>71</sup> Still, bearing all these limitations in mind, the net clinical benefit of noninvasively assessing CAD in ESRD by MDCT is important, since conventional angiography is an invasive method which requires hospitalization, raising concern issues regarding a higher risk of arrhythmias, stroke, cholesterol embolism, coronary artery dissection, or even death.<sup>68</sup>

## 6 | INTRA-VASCULAR ULTRASONOGRAPHY AND OPTICAL COHERENCE TOMOGRAPHY

### 6.1 | Intra-vascular ultrasonography (IVUS)

Intra-vascular ultrasonography can provide a comprehensive assessment of coronary plaques, yielding information beyond routine coronary angiography. In order to better identify certain components of coronary plaques, integrated backscatter IVUS has been developed and validated with histological findings.<sup>72,73</sup> High lipid content in the coronary plaques is an independent predictor of CV events in CAD patients.<sup>74</sup>

Limited data are available regarding the use of IVUS in ESRD. Miyagi et al compared plaque composition assessed by IVUS between two groups of patients (eGFR > 60 and <60 mL/min) and proved that impaired renal function is associated with higher lipid and lower fibrous volume.<sup>75</sup> The same influence of low GFR was observed in hypertensive and diabetic patients.<sup>73</sup> Furthermore, progressively declining GFR is an independent predictor of plaque burden, length, and risk for rupture.<sup>76</sup>

In CKD and ESRD patients, studies proved that IVUS-guided PCI reduced the contrast volume, incidence of contrast-induced acute kidney injury, and induction of renal replacement therapy at 1 year, when compared to angiography-guided PCI. Despite these positive results, IVUS-guided PCI did not reduce 1-year mortality in this population.<sup>77,78</sup>

Recently, the concept of low contrast volume PCI in ESRD was presented by the pilot study conducted by Ali ZA et al<sup>79</sup> The group performed zero contrast PCI 1 week after performing IVUS, with pre- and post-measurements of fractional and coronary flow reserve, confirming good results without serious complications.

### 6.2 | Optical coherence tomography (OCT)

Optical coherence tomography is another intra-coronary diagnostic technique with a better spatial resolution than IVUS. It has become extremely useful in cardiac catheterization laboratories in approaching high-risk lesions, as it provides important information about coronary morphology, plaque distribution and composition, and neointimal and thrombus assessment. Furthermore, it can help for PCI guiding and stent sizing. OCT-guided PCI seems to be similar to IVUS-guided PCI and both are superior to angiography-guided PCI, lowering the need for revascularization and the risk of cardiac death at 1 year.<sup>80,81</sup>

The use of OCT in patients with ESRD may help decrease the contrast volume and the risk of acute kidney injury. Case studies have reported promising results for novel methods such as zero contrast OCT-guided PCI. Karimi et al<sup>82</sup> used a mixture of saline and colloid to displace blood in order to perform OCT and guide PCI in a 67-year-old patient with an eGFR of 13 mL/min. Azzalini et al<sup>83</sup> performed PCI using dextran-based OCT guidance, with promising results.

Also, given that OCT is the only intra-vascular method capable of accurately imaging calcium thickening without artifacts, it could represent a reasonable alternative for ESRD patients, taking into account the limitations of MDCT.<sup>80</sup> Chin CY et al<sup>84</sup> investigated 62 HD patients by OCT and observed that in comparison with controls, HD-dependent patients had a higher calcium burden with extensively calcified coronary arteries and higher prevalence of nonatherosclerotic intimal calcium.

## 7 | CARDIAC MAGNETIC RESONANCE (CMR)

Myocardial fibrosis, one of the cornerstones in the pathophysiology of uremic cardiomyopathy, is caused by the activation of several biological pathways that end in cellular apoptosis. As renal impairment progresses, fibrosis advances, leading to diastolic and systolic dysfunction and congestive heart failure. In ESRD, myocardial fibrosis is an arrhythmogenic substrate causing ventricular reentering arrhythmias; this may explain the high prevalence of SCD in this population.<sup>85</sup> Increased amounts of uremic toxins and an imbalance in the activity of parathyroid hormone promote different forms of cardiac fibrosis. Fibrosis not only compromises the contractile performance, but also hampers intercellular coupling, slows conduction, and thereby increases the propensity to develop ventricular arrhythmias.

Cardiac magnetic resonance has emerged as a promising imaging modality for detecting myocardial fibrosis and is currently used for

the diagnosis of certain cardiomyopathies. For the general population, the best described technique is based on the delayed washin and washout of the contrast agent from the tissues with increased extracellular space—late gadolinium enhancement (LGE). In advanced CKD, the usage of gadolinium based contrast agents (GBCA) should be considered individually as it is limited by the risk (<1%) of developing a potentially lethal condition, nephrogenic systemic fibrosis (NSF).<sup>86,87</sup> In the past years, it was shown that persons with normal renal function can also develop NSF when exposed to GBCA, but until the exact pathophysiology of GBCA-induced disease is better understood, alternative gadolinium-free methods should be used whenever possible in advanced CKD.<sup>87,88</sup>

Native T1 is a novel noncontrast CMR technique based on the longitudinal recovery time of hydrogen atoms following their excitation. In any given magnetic field strength, every tissue will produce a specific range of values. Prolongation of myocardial relaxation time can appear secondary to fibrosis, amyloid, or edema.<sup>86</sup> Several studies have investigated its possible applications in ESRD as a surrogate for myocardial fibrosis.

Graham-Brown MPM et al compared native T1, systolic strain, and cardiac function of 35 HD patients and 22 controls, showing that in HD patients, native T1 is significantly prolonged and associated with reduced systolic, global longitudinal and circumferential strain, especially in the interventricular septum (IVS). This finding suggests that in HD patients, the grade of myocardial fibrosis may be greater in the IVS when compared to controls.<sup>85</sup> The same authors report the method is reproducible and unaffected by fluid variability between dialysis sessions.<sup>89</sup>

Rutherford et al studied a very similar cohort consisting of 33 HD patients and 28 controls and showed that global, septal, and mid-septal native T1 is significantly higher in HD patients. Also, native T1 correlates with LV mass, suggesting that as LVH progresses in severity, the underlying tissue abnormalities simultaneously develop. Interestingly, there was an association between higher septal T1 time and longer QT interval, a risk factor for ventricular arrhythmias and SCD. Additionally, the authors proved that GLS correlates with galectin-3, a novel marker of myocardial fibrosis.<sup>90</sup>

There are certain limitations of using native T1 in HD patients. First of all, there is no histological study demonstrating its correlation with myocardial fibrosis in this population. Moreover, inflammation, iron, and water content can influence native T1, which is extremely important given the chronic inflammation status and fluid variability between patients in ESRD.<sup>85</sup>

Another noncontrast CMR method, T1rho, also referred to as the spin-lattice relaxation time in the rotating frame, was proposed by Wang et al. T1rho has been already used to study intra-articular cartilage, brain, and liver and has the ability to characterize the interaction between tissue components, such as water and macromolecular compositions—collagen and proteoglycans. In ischemic heart disease, it was shown to be able to distinguish normal from infarcted myocardium and detect myocardial fibrosis. Based on this assumption, the team conducted a study on 32 asymptomatic HD patients and 35 healthy volunteers and showed that T1rho

values are significantly higher in ESRD patients with no history of cardiac disease, despite of having similar native T1 time with controls. Also, they detected higher T1rho values in patients with systolic and DD.<sup>91</sup>

Dobutamine stress CMR was shown to be useful for identifying significant CAD prior to potential RTx in high-risk patients—sensitivity 100%, specificity 89%.<sup>92</sup>

Since imaging the right ventricle can be challenging with ETT, CMR has been shown to be able to better assess it. Subclinical RV dysfunction can be detected early by CMR, and it is associated with a worse prognosis. Also, the duration of dialysis is an independent predictor of RV dysfunction.<sup>93</sup>

## 8 | CONCLUSIONS

Multi-modality cardiac imaging may provide both the cardiologist and the nephrologist insight into the cardiac involvement in ESRD in order to ease the early diagnosis and risk stratification. TTE remains the first-line investigation to assess cardiac function in CKD, but encompassing in our daily practice the newer approaches such as speckle-tracking imaging or CMR can guide us to a more comprehensive understanding of CVD in ESRD. This may lead to the development of new therapeutic strategies capable of improving CV outcomes in ESRD.

## DISCLOSURES

None.

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