

Role of Acoustic Radiation Force Impulse (ARFI) elastography and renal doppler in the evaluation of chronic kidney disease

Dr.H Nadeem ur Rahman¹, Dr. Ayush Gupta² , Dr.Meenakshi Ahuja³

¹Senior resident, Department of Radiodiagnosis and Imaging, All India Institute of Medical Science, Bhopal

² Senior Resident, Department of Radiodiagnosis and Imaging, All India Institute of Medical Science, Bhopal

³ Senior Resident , Department of Radiodiagnosis and Imaging, All India Institute of Medical Science, Bhopal

Corresponding author: Dr. H Nadeem ur Rahman

Abstract:

Introduction: Chronic kidney disease is a progressive condition that affects >10% of the general population worldwide and has emerged as one of the leading causes of mortality worldwide. The diagnosis and staging are based on the clinical and biochemical assays. Shear wave elastography is an emerging ultrasound technique that has a potential role in assessing the severity of CKD. However, it is still in the preliminary phase and has yet to be incorporated into the guidelines. Hence, the main purpose of our study is to evaluate the role of shear wave elastography utilizing acoustic radiation force impulse technique in assessing the severity of CKD and to evaluate whether there is any correlation between renal SWV values with serum creatinine, estimated glomerular filtration rate, and renal resistive index.

Method: A prospective observational study of comparative cross-sectional design with analytical component comparing two groups, one group being clinical and biochemically proven case of CKD and the other group comprising non-CKD patients. There were 106 patients, with 52 being known cases of CKD and the other 54 being non-CKD patients. Shear wave velocity and renal resistive index were measured in these two groups, and a correlation between SWV, RRI, serum creatinine, and eGFR was made.

Results: A cutoff kidney shear wave speed value of 2.49 m/s could be used to discriminate the diseased group from the non-diseased group with a sensitivity, specificity, PPV, NPV, and accuracy of 84.62%, 87.04%, 86.27%, 85.45% and 85.85% respectively and the mean shear wave velocity decreased with the decrease in eGFR and the mean SWV among the CKD groups were 2.51 ±0.26 m/s for stage 2, 2.34 ±0.25 m/s for stage 3A and 2.24±0.28 m/s for stage 3B and 1.98±0.21 m/s for stage 4 of CKD. There is also a linear positive correlation between SWV and renal resistive index. Renal shear wave velocity values decreased with the increase in serum creatinine and a decrease in the estimated GFR. There was a statistically significant difference between renal SWV values in patients with an estimated GFR greater than 90 mL/min/1.73m² compared to patients with stage 4 or 5 CKD (estimated GFR, <30 mL/min/1.73m²).

Conclusion: Our study showed that renal shear wave velocity (SWV) values estimated by ARFI elastography showed a statistically significant difference between patients with CKD and those with normal renal functions. In patients with CKD, the SWV values showed a progressive decline with deterioration of eGFR vis-a-vis an increase in the severity of CKD. A cut-off SWV value of 2.49 m/s or less could differentiate the CKD group from the non-CKD group while having good sensitivity and specificity. Our study also showed that along with RI, SWV values were also found to be helpful in predicting the progression of CKD. Thus, ARFI elastography along with renal Doppler (in addition to

eGFR) evaluation is a potential adjunct imaging method for assessing patients with CKD, especially in the case of diabetic nephropathy where conventional US findings can be equivocal.

Introduction:

Chronic kidney disease (CKD) is a progressive loss of renal function whose principal causes include hypertension, diabetes, and primary renal disorders such as nephrotic syndrome, glomerulonephritis, etc. As CKD advances, it results in widespread tissue scarring, which subsequently leads to the destruction of renal parenchyma and end-stage renal failure. The pathologic damage is irreversible and can lead to significant morbidity and mortality. CKD poses a major public health problem in developed as well as developing countries like India(1). Hence, screening and early detection of CKD is of paramount importance so that appropriate measures can be taken to arrest its progression to end-stage disease, which is expensive to treat and associated with a significant decline in the patient's socio-economic profile. Traditional techniques have been employed to identify and assess renal diseases. These include conventional ultrasonography, CT, MRI, and blood sample biochemical analyses. However, these methods carry their risks, such as radiation exposure and the administration of iodinated contrast medium in CT scans. Conventional renal ultrasound is often used in the initial evaluation because it is safe, easy, and inexpensive. Renal sonographic features can be easily assessed, such as increased parenchymal echogenicity and decreased renal size and parenchymal thickness. Parenchymal echogenicity is a commonly used marker for nephropathy. However, this is subjective, not quantitative, and often fails to detect renal abnormality. Thus, conventional renal ultrasound is usually equivocal in evaluating the progression of CKD.(2)

The estimated glomerular filtration rate (eGFR) derived from serum creatinine readings using one of several formulas is now used to categorize CKD into five severity-based stages.(3) Acute alterations in kidney function, a high protein diet, an extreme body size, and severe liver illness are just a few clinical scenarios when eGFR readings may become inconsistent. The kidney's histology impacts its mechanical characteristics, precisely the degree of fibrosis in the parenchyma. As a result, renal biopsy continues to be the best method for histologically evaluating fibrosis. (4). The invasive procedure could result in post-biopsy problems like bleeding. Therefore, there is a great interest in creating non-invasive techniques to assess nephropathy precisely.

Shear wave elastography (SWE) by Acoustic radiation force impulse (ARFI) technique is an emerging ultrasound technique used to assess tissue stiffness. A real-time, short-duration brief acoustic push pulse generates shear waves that propagate perpendicular to the main US beam. When the waves hit the targeted tissue, the tissue is "pushed" in the direction of propagation, causing it to deform or displace temporarily and the velocity of shear wave propagation is proportional to the tissue stiffness. (5). The ultrasound scanner can monitor the tissue displacement, measuring the time-to-peak displacement and the recovery time. The parameters are expressed in kilopascals (kPa) or velocity (m s⁻¹) pressure units. Currently, elastography is employed in multiple organs such as liver, breast, prostate, etc. One such approved and commonly used indication is evaluation of hepatic fibrosis and staging of CLD.(5-7) .

The Doppler evaluation of kidneys also plays a crucial role in the evaluation of the progression of CKD. The renal resistive index acts as an independent prognostic marker in the progression of CKD (8). Resistive index (RI) indirectly measures microcirculation resistance/ impedance (9). It represents the sum of the resistive forces opposed to blood pulsatile flow into arteries. In Chronic kidney disease, progressive glomerular atrophy, renal mass loss, and tubular-interstitial fibrosis are responsible for the

reduction in renal blood flow, thus decreasing the amplitude of the spectral wave profile and increasing the intrarenal resistance and therefore resulting in the rise of RI values (>0.7).

It has been observed from a few previous studies of liver fibrosis. (6,7) That hepatic stiffness increases with the progression of liver disease. Considering these data, it can be hypothesized that similar changes occur in the renal tissues; thus, the progression of CKD as measured by the decrease in the estimated GFR should lead to an increase in renal shear wave velocity. However, recently published data (10,11) Showed that the renal SWV decreases with the decrease in the estimated GFR and is possibly related to the intra-renal hemodynamic changes(11).

Thus, because data about the relationship between renal SWV and doppler parameters such as RI are scarce, our study aimed to determine whether renal SWV assessed by ARFI elastography and renal resistive index can predict CKD progression as reflected by a decrease in eGFR.

Our study also aimed to investigate whether renal shear wave velocity could be used as an indicator to distinguish between normal and abnormal renal parenchymal tissue and to assess the correlation between elastography and various parameters such as eGFR, serum creatinine, and renal resistive index.

Materials and methods:

Participants :

Our study included patients with and without CKD whose renal SWV by ARFI elastography and renal resistive index were evaluated between March 2021 and October 2022. In our study, we included a total of 106 prospective participants, of whom 52 were patients with different stages of CKD diagnosed and receiving treatment in the internal medicine and nephrology department. The patients with structural renal diseases such as renal calculi were not included in our study, and 54 were controls (non-CKD group). The participants in the control group were either patients with no history of kidney disease, with an eGFR of greater than 60 mL/min, and no abnormal renal markers or regular healthy volunteers.

The patients with CKD were diagnosed based on the criteria from the National Kidney Disease Foundation guidelines (12)- estimated glomerular filtration rate (GFR) of less than 60 mL/min, the presence of markers of renal damage, such as a urinary albumin-to-creatinine ratio (UAC) of greater than 30 mg/g for more than three months, or both.

All participants had previously undergone a conventional renal US examination, and we excluded those who had a renal parenchymal thickness of less than 1 cm and those with renal cortex-to-skin surface depth of more than 8 cm. For all of our patients with CKD, we recorded the age, sex, body mass index (BMI), presence/absence of diabetes mellitus, presence/absence of hypertension, underlying causes of CKD (if present), and estimated GFR.

We calculated the estimated GFR using the Chronic Kidney Disease Epidemiology Collaboration formula,(13) And patients with CKD were classified as follows:

Stage of CKD	eGFR
G1	>90 mL/min*
G2	60 to 89 mL/min*
G3	30 to 59 mL/min
G4	15 to 29 mL/min
G5	<15 mL/min

*stages G1 and G2 (estimated GFR > 60 mL/min) but had other markers of renal damage (albumin excretion rate > 30 mg/24 h and histologic abnormalities) documented for more than three months. All participants included in our study signed an informed consent form.

The study was approved by the local Ethics Committee and was conducted by the Declaration of Helsinki of 1975

Acoustic Radiation Force Impulse Elastography

The ARFI elastography was performed with Acuson S2000 US system (Siemens AG), Virtual Touch quantification (VTTQ) software version 2.0, with a 4C1 1.6-MHz convex transducer. The examination was in lateral decubitus position with the right arm maximally abducted & extended. The probe was placed steadily with minimum compression, and the person was asked to hold their breath in full inspiration for a few seconds to minimize respiratory motion. The long-axis image of the kidney was obtained through intercostal space and was assessed through the midsagittal/longitudinal approach.

The anatomic region of interest is analysed using a “region of interest” (ROI) cursor measuring 10X5mm (dimensions predefined by the manufacturer) placed simultaneously with real-time B-mode imaging. The ROI cursor was placed in the renal cortex in the middle third of the kidney, excluding the medulla as much as possible, with the central axis of the ROI box lying as parallel as possible to the central axis of the medullary pyramids in the mid pole and the “Update” button was pressed for quantification, and the renal cortical shear wave velocity was obtained in m/s. Similarly, then the ROI cursor was placed in the upper pole and lower pole cortex through midsagittal/coronal approach three values at each pole were taken and mean values are calculated.

The then resistive index was measured at the interlobar artery level by turning on the color Doppler box, and then spectral tracings were recorded. Three values were taken and mean was calculated. Below figure shows the method of acquiring SWV.



Figure 1 Demonstrates the technique of assessment of shear wave velocity.

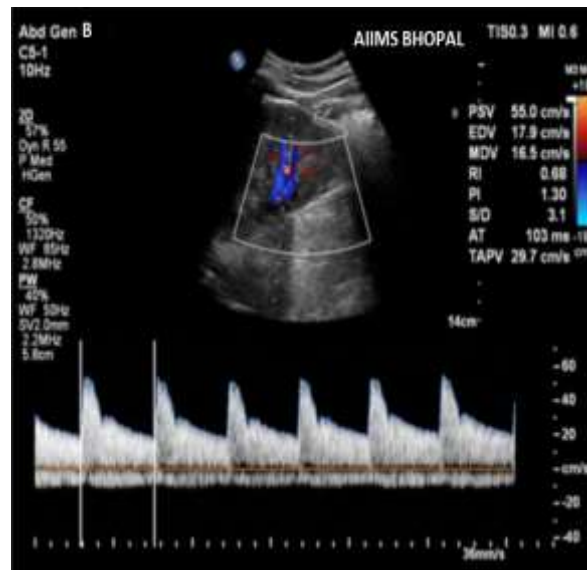


Figure 2a- showing method ROI cursor placement values and obtaining SWV values Figure 2b showing method of obtaining RI values and obtaining SWV values from the intralobar artery.

Statistical analysis:

Data collected was entered into Excel sheets primarily (Microsoft Excel 2010) and then transferred after data cleaning and rechecking to Epi-info software (Epi Info version 7.2) for analysing. Continuous data was expressed as the mean (standard deviation). The mean shear wave velocity and renal resistive index among diseased and control groups was analysed using one-way analysis of variance (ANOVA) and the Tukey post hoc test. Correlations between SWV and resistive index with serum creatinine, eGFR was analysed using Pearson's correlation coefficient ($p \leq 0.05$). The diagnostic performance of SWE imaging and resistive index in distinguishing the diseased group from the control group was assessed by receiver operating characteristic (ROC) curves. The optimal cut-off values for the prediction of the control group were chosen to maximize the sum of sensitivity and specificity. Statistical tests were performed on the data collected and significance levels was declared at $p \leq 0.05$

RESULTS:

We studied 106 patients with or without CKD in which the renal SWV by ARFI elastography and resistive index values were taken and analysed. In our study, we evaluated a total of 52 patients with CKD, of whom 25(48%) were male and 27 (52%) were female. The patients age ranged from 19-68 years with a mean age of 48.2 years.

The difference between mean of two groups (cases vs controls) were compared by student t test. The mean shear wave velocity among cases is 2.19 ± 0.30 m/s and mean SWV among controls is 2.51 ± 0.31 and the mean RI among cases is 0.75 ± 0.05 and mean RI among controls is 0.60 ± 0.05 (p value < 0.001). Thus, the mean SWV and RRI is significantly higher in CKD patients when compared to non-CKD group. (Table 1)

We also found the mean SWV among the different stages of CKD which were 2.51 ± 0.26 m/s for stage 2, 2.34 ± 0.25 m/s for stage 3A and 2.24 ± 0.28 m/s for stage 3B and 1.98 ± 0.21 m/s for stage 4 of CKD reflecting the progressive rise in SWV values as the CKD stage advances. (Table 2).

The mean shear wave velocity among the non-CKD groups were 2.51 ± 0.31 ms and the mean SWV

values of early stage (stage 2) CKD were 2.51 ± 0.26 m/s, thus resulting in considerable overlap between non-CKD group and early-stage CKD.

The mean RI among the CKD groups were 0.71 ± 0.02 for stage 2, 0.71 ± 0.03 for stage 3A 0.74 ± 0.04 for stage 3B and 0.80 ± 0.04 for stage 4 of CKD reflecting the positive correlation between RI and stage of CKD. (Table 2)

For a cutoff value of 2.49 m/s or less, renal SWV had 84.62% sensitivity, 87.04% specificity, 86.27% % positive predictive value, and a 85.45 % negative predictive value (area under the receiver operating characteristic curve, 0.79; P = .001) for predicting the presence of an estimated GFR of less than 60 mL/min/1.73m². (Figure 3)

We performed correlations between SWV with the serum creatinine levels, estimated GFR and renal resistive index. we found positive correlation of SWV with renal resistive index (r value-0.524 and p value <0.001), eGFR value (r value-0.554 and p value <0.001), and negative correlation with serum creatinine (r value-0.554 and p value <0.001).

Table 1 Comparison of shear wave velocity and Resistive index between cases and controls

	Cases	Controls	P value
Shear wave velocity	2.19 ± 0.30	2.51 ± 0.31	<0.001
Resistive index	0.75 ± 0.05	0.60 ± 0.05	<0.001

Table 2: Mean Kidney Shear Wave Speed Values According to estimated GFR and stage of CKD

		N	Mean	SD
Mean SWV	Stage 2	6	2.51	0.262
	Stage 3A	10	2.34	0.256
	Stage 3B	17	2.24	0.283
	Stage 4	19	1.98	0.216
Resistive index	Stage 2	6	0.71	.022
	Stage 3A	10	0.710	.034
	Stage 3B	17	0.742	.044
	Stage 4	19	0.809	.046

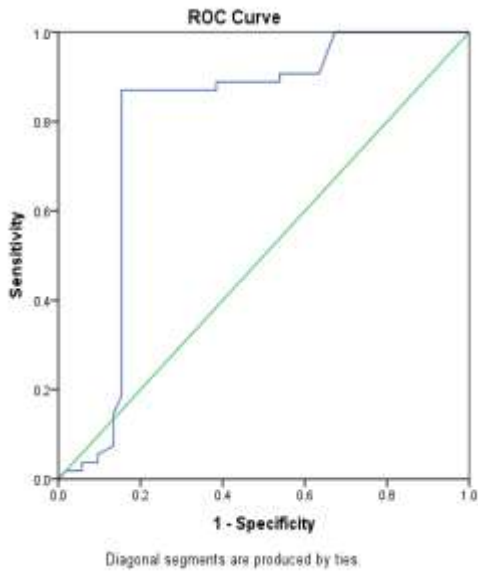


Figure 3 showing ROC curve of shear wave velocity in differentiating between case and controls.

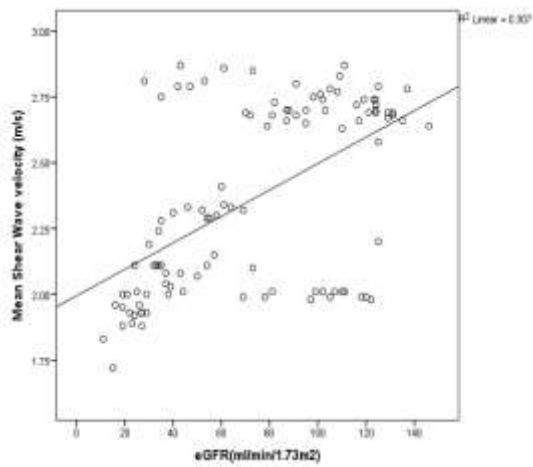


Figure 4-scatterplot showing correlation between between SWV and eGFR

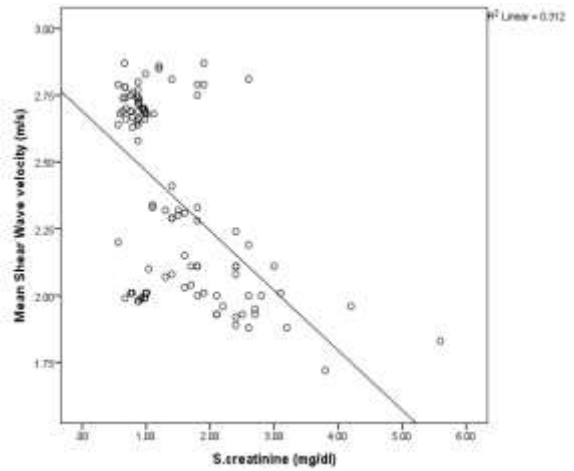


Figure 5-scatterplot showing correlation between SWV and serum creatinine

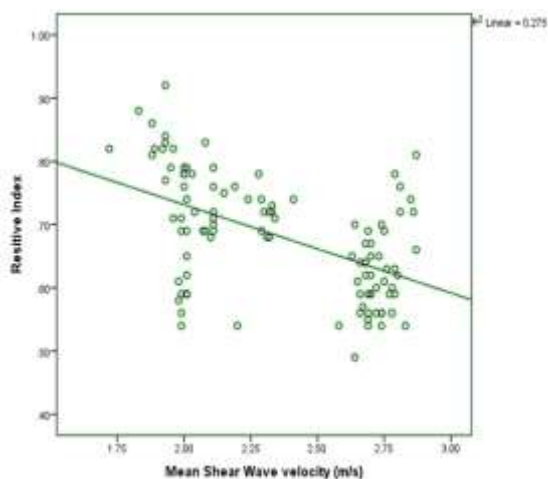


Figure 6 scatterplot showing correlation between RI and SWV.

DISCUSSION:

The renal assessment for staging and diagnosis of CKD by means of conventional US is highly subjective, qualitative and operator dependent. There have been some attempts at characterizing renal echogenicity, parenchymal thickness, and renal length as markers of chronic disease(14). However, data are still scarce regarding the classifications and cutoff values.

In our study, the total sample size comprised of 106 individuals, of which 52 were a known case of CKD and other 54 patients were healthy individuals. Similar multiple studies also have taken place such as one conducted by Guo et al (10) which comprised of 327 healthy volunteers and 64 CKD patients.

The elastography has emerged as a quantitative, non-invasive tool that has commonly used and also standardized in some of the guidelines for evaluation of the hepatic fibrosis(15)

In ARFI (VTTQ technique, Siemens) elastography, for chronic liver diseases, SWV showed a good positive correlation with the stage of liver fibrosis(16). Kircheis et al.(17) observed that hepatic tissue stiffness values increased significantly as fibrosis evolves. Mean SWV was 1.09 ± 0.13 m/s for patients with no significant fibrosis, 1.44 ± 0.26 m/s for patients with significant hepatic fibrosis, and 2.55 ± 0.77 m/s for patients with end stage liver cirrhosis, respectively.

The administration of doppler, most importantly renal resistive index to the assessment of CKD serves as an independent predictor of prognosis.(8) Resistive index (RI) is an indirect measure of microcirculation impedance (9). It is measured as Resistive Index = $(PSV - DV) / PSV$, where PSV – peak systolic velocity, DV- Diastolic velocity. The normal value in young patients is ≈ 0.60 . A RI = 0.70 is generally considered as the normal upper limit.

In Chronic kidney disease, the progressive glomerular atrophy, renal mass loss and tubular-interstitial fibrosis are responsible for reduction in renal blood flow, thus decreasing the amplitude of the spectral wave profile and resulting in an increase of RI values $> 0.75-0.80$ owing to high arterial stiffness, atherosclerotic eutrophic remodelling of small renal vessels and microcirculation rarefaction (18).

Boddi et al [20], have demonstrated recently that RI allows the early diagnosis of chronic tubular-interstitial nephropathies. In a recent study performed on 86 patients with CKD, the authors reported a marked GFR reduction in patients who demonstrate an initial RI > 0.70 , while kidney function decreased more slowly in patients with an initial value of RI ≤ 0.61 or in the range between 0.62 and 0.69. Therefore, an RI ≥ 0.70 is predictive of a poor prognosis and progression of CKD, independently

of the initial assessed GFR (8). Our study showed, there is a linear relationship with the RI and stage of CKD and the mean RI shows statistically significant difference between CKD and non-CKD groups. There is also linear positive correlation between SWV and RI.

In contrast to such findings for chronic liver diseases, the SWV in CKD patients was significantly lower than that in healthy controls in our study. The reason for this difference remains unclear. Some scholar speculated that it is because the kidney is an organ with rich perfusion, receiving 20% of cardiac output despite only constituting <1% of body mass (19). Its distension and stiffness may therefore be significantly affected by renal blood perfusion. Under normal conditions, in order to provide the large quantity of oxygen necessary to support massive levels of reabsorption, the renal tubules are surrounded by a dense vascular plexus in both the cortex and medulla(19). As CKD progresses, glomerular sclerosis, tubular atrophy, and peritubular fibrosis gradually become aggravated. Accordingly, the blood flow in the peritubular vascular plexus decreases. Considering the remarkable extent of damage in the microcirculation in advanced CKD, it is conceivable that renal blood flow may significantly influence SWV values, perhaps even more than interstitial fibrosis.

Asano et al.(11) reported the degree of interstitial fibrosis in the kidneys of CKD is not as marked as that in chronic liver disease and suspected interstitial fibrosis is not the main affecting factor of ARFI elastography in the kidneys tissue elasticity. In the kidney, point SWE has been researched mainly by use of the ARFI (VTQ technique) which showed that kidney SWV values decreased with the progression of CKD (20). Our study also substantiated the similar findings. In addition to this our study also includes the assessment of renal hemodynamic status via the renal resistive index parameter as many of the renal pathologies predominantly cause initial hemodynamical alteration earlier in the course of disease than the pathological fibrosis. In our study in addition to the correlation of SWV with renal biochemical profile, we attempted to correlate the renal resistive index parameter, a marker of microvascular impedance with shear wave velocity and the renal bio-chemical marker.

Our study showed good correlation between renal resistive index and SWV. Thus, potentiating the use of RI and SWV for staging the CKD along with the conventional sonographic parameters such as renal length and cortical thickness. Compared with the study by Guo et al (10), we tried to find a renal SWV cutoff value to differentiate between patients with and without moderate and severe alteration of kidney function. In our study, we found that for a cutoff kidney shear wave speed value of 2.49 m/s could be used to discriminate the diseased group from non- diseased group with a sensitivity, specificity, PPV, NPV and accuracy of 84.62%, 87.04%, 86.27%, 85.45% and 85.85% respectively. This finding implies that this method can be used as good discriminating parameter in unequivocal states of CKD such as diabetic nephropathy where the conventional US parameter such as renal length is generally not reduced until in the late course of disease.

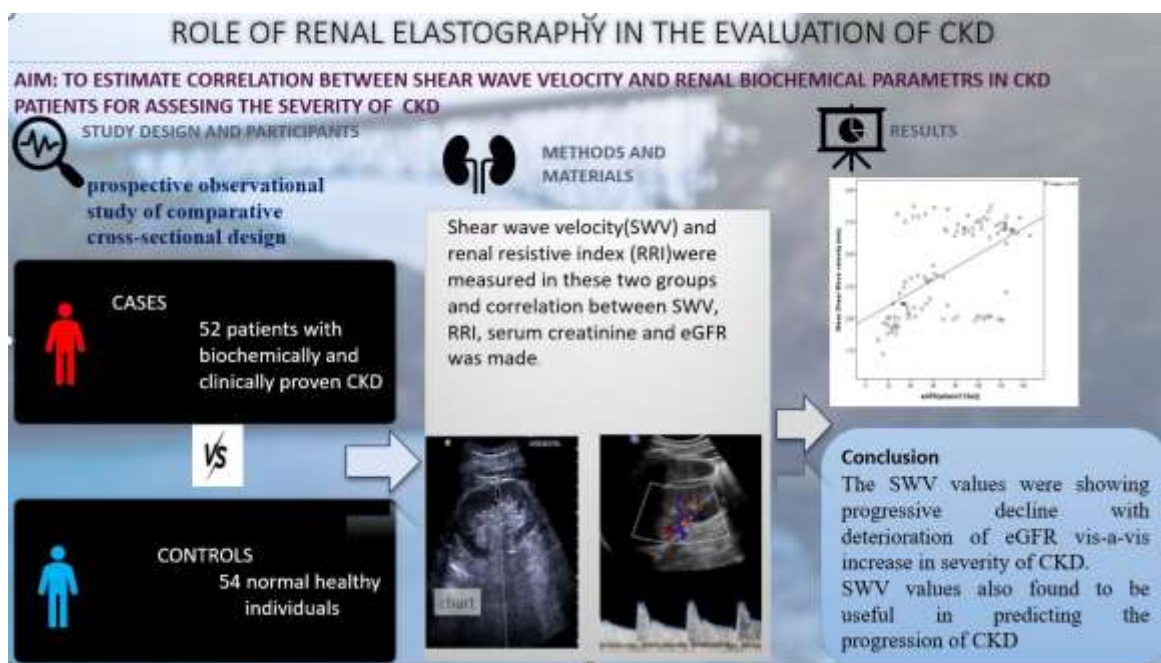
In our study, we found that kidney shear wave velocity values decreased with the increase in serum creatinine and decrease in the estimated GFR, and there was a statistically significant difference between renal shear wave velocity values in patients with an estimated GFR of greater than 90 mL/min/1.73m² compared to patients with stage 4 or 5 CKD (estimated GFR, <30 mL/min/1.73m²). In our study, we obtained the mean shear wave velocity among the CKD groups were 2.51 ±0.26 m/s for stage 2, 2.34 ±0.25 m/s for stage 3A and 2.24±0.28 m/s for stage 3B and 1.98±0.21 m/s for stage 4 of CKD. These findings are reflecting the potential use of ARFI technique for staging the CKD as there is linear correlation between SWV and clinical and biochemical staging of CKD.

However, there is heterogeneous distribution of sample such as lesser number of patients in stage 2 CKD than stage 4 CKD. Further study with homogenous sample size in each group and larger population may be fruitful in proving the hypothesis. Our results revealed that the mean SWV of the renal parenchyma had statistical difference between the health volunteers and with different group in CKD patients (all P<0.001). SWV values correlate significantly with serum creatinine ($r=-0.559$, P=0.001), and glomerular filtration rate ($r=0.554$, P=0.001). Similar result was demonstrated in Guo et al.'s

evaluation that the SWV correlate significantly with e-GFR ($r=0.3$, $P=0.01$), serum urea nitrogen ($r=0.3$, $P=0.001$) and creatinine ($r=0.41$, $P=0.001$) (10).

Conclusion:

In conclusion, our study showed that renal shear wave velocity (SWV) values estimated by ARFI elastography showed statistically significant difference between patients with CKD compared to patients with normal renal functions. In patients with CKD, the SWV values were showing progressive decline with deterioration of eGFR vis-a-vis increase in severity of CKD. Our study also showed that for a cut off value of SWV of 2.49 m/s or less, we could differentiate the CKD group from non-CKD group, while having a good sensitivity and specificity. Our study also showed that along with RI, SWV values also found to be useful in predicting the progression of CKD. Thus, ARFI elastography along with renal doppler (in addition to eGFR) estimation is a potential adjunct imaging method for assessing patients with CKD especially in case of diabetic nephropathy where conventional US findings can be equivocal.



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