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## Shear wave elastography in transplant kidney and its correlation with renal doppler parameters and eGFR

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### Abstract

Chronic allograft nephropathy is the most common cause of graft failure and is characterized by interstitial fibrosis and tubular atrophy, this study evaluated the role of shear-wave sonoelastography in the differentiation of stable renal allograft from allograft dysfunction & establish the correlation of parenchymal stiffness values with resistive index (RI), serum creatinine level, estimated glomerular filtration rate (eGFR). A prospective study of 40 patients who had undergone renal transplantation was conducted between October 2018 and July 2020. Patients were classified as having stable allograft and allograft dysfunction on the basis of clinical parameters practised in our institution. Receiver operating characteristic curve were drawn to obtain a cut off value with maximum sensitivity and specificity. Pearson's correlation was used to evaluate different renal parameters and their correlation with the shear wave elastography (SWE) value. In this study 27 patients had graft dysfunction and 13 had stable graft. Use of the threshold value of 8.23kPa for SWE resulted in a sensitivity of 70% and specificity of 100% for the differentiation of stable allograft from allograft dysfunction. Parenchymal stiffness showed inverse correlation with eGFR ( $r = -.756, P < 0.001$ ) and a direct correlation with RI ( $r = 0.42, P = 0.003$ ) and serum creatinine level ( $r = 0.76, P < 0.001$ ).

SWE helps to differentiate stable allograft from allograft dysfunction. The direct correlation with RI & serum creatinine level and inverse correlation of parenchymal stiffness with eGFR show that SWE reflects functional status of the renal allograft.

**Keywords:** chronic allograft rejection, interstitial fibrosis, shear wave elastography (SWE), resistive index (RI), estimated glomerular filtration rate (eGFR)

### Introduction

With increase in number of end stage renal disease, rate of renal transplant is increasing as it is more cost effective in long term and less traumatic with improved life quality as compared to haemodialysis. However, renal allograft loss due to chronic rejection is a major problem which often presents as progressive and insidious allograft dysfunction characterized by slow loss of renal function.

Currently, biopsy remains the gold standard for assessing renal allograft dysfunction, including estimating fibrosis. Being an invasive process, it is not routinely done until patient starts to show features of failure like rise in serum creatinine or proteinuria.

However, biopsy remains an imperfect standard, with limitations and inherent risks, including sampling errors, allograft trauma sustained with multiple needle pass attempts, and large interobserver variation in interpreting biopsy samples among pathologists. Furthermore, biopsy is neither reasonable nor feasible for every fluctuation in the renal allograft status. Complications of biopsy include bleeding (ranging from gross haematuria to perirenal hematomas), arteriovenous fistula formation, infection, and pseudoaneurysms<sup>[1]</sup>. Chronic rejection term has been replaced with more histologically descriptive term "interstitial fibrosis and tubular atrophy" and often presents as progressive and insidious allograft dysfunction characterized by a slow loss of renal function. It may manifest as new or worsening hypertension, an increasing serum creatinine level, a down trending estimated glomerular filtration rate, or proteinuria<sup>[2-4]</sup>. Unfortunately, serum indicators of declining renal function often lag behind actual graft damage, at which point the injury may be irreversible<sup>[1]</sup>.

Elastography imaging is the newer modality which can be added to routine B mode ultrasound. It allows us to quantitatively assess the tissue stiffness by assessing the change in tissue elasticity due to pathological process. Quantitative methods of elastography measurement are well established in the liver fibrosis patient population, for both screening purposes and monitoring disease progression.

## 2. Material and Method:

A prospective study of patients with renal transplant was conducted after approval by the institutional ethics committee. Informed and written consent was obtained from all the patients.

The study was conducted at Jagadguru Sri Shivarathreshwara Hospital, Mysore, India.

### 2.1 Inclusion criteria

1. Post-transplant patient referred to the radiology department for ultrasound examination due to clinical indication or for routine follow-up.
2. Patient with more than 12 months of duration post transplantation.

### 2.2 Exclusion criteria

1. Surgical site infection.
2. Patients with perirenal collection.
3. Urinary tract obstruction.
4. Patients with renal artery stenosis.
5. Patients within 12 months and after 36 months of post transplantation.

### 2.3 Technique

A total of 40 patients were examined. All patients were subjected to routine ultrasound examination followed by Doppler interrogation of renal artery by spectral Doppler and shear wave elastography using Philips iU22 ultrasound equipment with a convex phased array probe C5-1 and frequency 1 – 5 MHz.

With patient lying in a supine position, B mode ultrasound was performed which provided an overview about the organ and its surrounding environment, including presence or absence of perinephric fluid collection, hydronephrosis.

Addition of color Doppler aids in the perfusion related diagnosis such as renal artery stenosis. Three RI values were acquired from the corresponding locations in renal segmental arteries (one from each upper, mid and lower polar region) and average of the three was included for the study.

The sampling for shear-wave sono-elastography was performed after the patient was instructed to breath normally. A total of six measurements of shear-wave sonoelastography, two each from the upper pole, lower pole, and mid-interpole regions—were performed and a valid reading recorded in kilopascals. A valid measurement is one where a numerical result is obtained, not an 0.00. The mean value of parenchymal stiffness was included for each patient. The tissue stiffness information (kPa value) was directly obtained from the sampling frame [Figure 1A-E].

eGFR was calculated using MDRD equation. It uses serum creatinine and patients characteristics such as patient age, gender (M/F) and ethnicity (Black/ white). Serum creatinine done within the seven days of ultrasound examination was taken for calculation.

A study by Catherine L Salvador *et al.* [5] has suggested that

MDRD equation is the most accurate of creatinine-based equation to calculate eGFR.

Grafts were categorized as stable or dysfunctional based on one time serum creatinine level of more than 1.2 mg/dL (protocol practised in our institution).

Software (SPSS, version 22.0) was used for the statistical analysis. The association of graft RI & parenchymal stiffness and eGFR & parenchymal stiffness was analysed by means of Pearson correlation.

Receiver operating characteristic curve was also drawn to evaluate the ability of parenchymal stiffness to enable differentiation of stable allograft from allograft dysfunction groups.

## 3. Result

Among 40 patients included in study, 34 were male and 6 were female. The age of the patients ranged from 21-61 years with mean age 39.15 +/- 11.70 years. Duration of transplant ranged from 12 months to 36 months with mean duration of transplantation 22 months. Average eGFR was 63.325 ml/min/1.73 m<sup>2</sup>, eGFR range is 13- 149 ml/min/1.73 m<sup>2</sup>.

RI range was 0.5-0.9 with average RI 0.705 +/- 0.08. There were 26 patients with RI less than 0.75 and 14 patients with RI more than 0.75.

The shear-wave elastography in 40 patients ranged from 5-19kPa with average value of 9.87kPa.

In this study, 13 patients with stable graft (creatinine less than 1.2mg/dL) had mean elastography value of 6.15kPa (range 5-8kPa). Rest 27 patients with unstable graft (creatinine more than 1.2mg/dL) had mean elastography value of 11.7kPa (range 5-19kPa)

Renal allograft parenchymal stiffness at shear-wave sonoelastography was significantly correlated with the RI (Pearson r= 0.42, P = 0.003) [Figure 2] and serum creatinine level (Pearson r = 0.76, P < 0.001) and inversely related with the eGFR (Pearson r = -.756, P < 0.001) [Figure 3]

The area under the curve for allograft parenchymal stiffness with a threshold of 8.23kPa was 0.899, with a 95% confidence interval of 0.80, 0.99 (P =.000) [Figure 4] to differentiate stable allograft from allograft dysfunction groups, with a sensitivity of 70.4% (19 out of 27) and specificity of 100% (13 of 13 patient).

In this study, all the patient (13 in number) with creatinine <1.2mg/dL have a elastography value of less than 8.23kPa with average elastography value of 6.15kPa.

However, we have 8 patients who have serum creatinine > 1.2mg/ dL and elastography value less than 8.23kPa.

Rest of the 19 patients have serum creatinine more than 1.2mg/dL and SWE value above 8.23kPa. [Table 1]

## 4. Discussion

Chronic allograft nephropathy is the most common cause of graft failure beyond the 1st year after renal transplantation and is highly prevalent in renal transplant recipients, with moderate to severe chronic allograft nephropathy present in 24.7% of recipients at 1 year after transplantation and in 89.8% of recipients by 10 years after transplantation [6].

For prompt patient management, early detection of allograft dysfunction is necessary, which is presently based on serum creatinine level, eGFR, and Doppler-based RI. This study was conducted to examine the role of US-based shear-wave sonoelastography-determined parenchymal stiffness as an additional tool in the evaluation of these patients.

In this study we tried to established the relation between elastography value, Doppler RI, serum creatinine and eGFR and we found that:

There is direct correlation between Doppler RI and elastography value ( $r = 0.42$ ). As the RI value increases, elastography value increases. However, there are multiple causes of increase in RI, such as – Renal artery stenosis, acute graft rejection and chronic graft rejection (secondary to parenchymal changes).

In this study, 27 patients who had graft dysfunction (serum creatinine  $>1.2\text{mg/dL}$ ) has average RI of  $0.73 \pm 0.08$ , while the other 13 with stable graft (serum creatinine  $<1.2\text{mg/dL}$ ) has average RI of  $0.65$  with standard deviation of  $0.05$  and correlation value  $p < 0.0001$ .

The RI is widely used in the assessment of renal transplant function and reflects the status of the allograft [7]. An RI less than  $0.7$  is normal, an RI higher than  $0.8$  is abnormal, and an RI of  $0.7-0.8$  is indeterminate. Boas *et al.* [8] reported that normal transplant kidneys have an average RI of  $0.71 \pm 0.11$ , and kidneys in acute rejection have an RI of  $0.77 \pm 0.11$ . Use of a cut-off of  $0.8$  resulted in a sensitivity of  $38\%$  and specificity of  $63\%$  for acute rejection. In that study [8], the mean RIs differed significantly between stable allograft and allograft with dysfunction. However, the difference between RIs in acute allograft dysfunction and chronic allograft dysfunction was not significant, which suggests that acute allograft dysfunction cannot be differentiated from chronic allograft dysfunction on the basis of RI.

Increased RI value cannot differentiate between these causes. Increased elastography value in such patients can guide for further investigation to rule out more chronic pathology.

In this study we also found that allograft parenchymal stiffness at shear-wave sonoelastography showed a significant correlation to serum creatinine value (Pearson  $r = 0.76$ ). This signifies that the allograft parenchymal status can reflect functional parameters of the allograft. However, Brocchi *et al.* [9] found no significant correlation between parenchymal stiffness and renal function (single serum creatinine value).

Arndt *et al.* [10] found that renal allograft parenchymal stiffness is inversely related to eGFR ( $r = 20.47$ ). In our study, we also found an inverse relationship between eGFR and allograft parenchymal stiffness at shear-wave sonoelastography ( $r = -.756$ ). Because an increase of parenchymal fibrosis leads to a deterioration of allograft function, the inverse character of this association is plausible from a clinical point of view.

Because of the superficial location of transplant kidney, allowing more accurate measurements several studies have been performed. In our study, the mean renal allograft parenchymal stiffness measured with shear-wave sonoelastography was  $9.82 \text{ kPa} \pm 4.36$  (range,  $5-19 \text{ kPa}$ ). The mean parenchymal stiffness values in stable allograft and allograft dysfunction were  $6.15 \text{ kPa} \pm 0.79$  and  $11.76 \text{ kPa} \pm 4.20$  respectively. In our study, use of the threshold value of  $8.23\text{kPa}$  resulted in a sensitivity of  $70\%$  and specificity of  $100\%$  for the differentiation of stable allograft

from allograft dysfunction.

In our study 13 patients with stable allograft showed elastography value of less than  $8.23\text{kPa}$ .

Among 27 graft dysfunctional group, 8 patients have elastography value less than  $8.23\text{kPa}$ . This can be attributed to the fact that the likelihood of fibrosis in patients with acute allograft dysfunction within the first few months after transplantation is relatively low, however there can be rise in serum marker such as serum creatinine. Among these 8 patients, 4 patients underwent renal biopsy and showed features of acute cellular rejection.

Remaining 19 patients had serum creatinine  $>1.2\text{mg/dL}$  and elastography value more than  $8.23 \text{ kPa}$ . Among these 19, 11 patients who underwent renal biopsy, 3 patients showed acute rejection with high elastography value, range –  $11.8-15.2\text{kPa}$ . As mentioned earlier the likelihood of fibrosis in patients with acute allograft dysfunction is relatively low, there might be other confounding factors that also resulted in increased parenchymal stiffness in acute allograft dysfunction. Gennisson *et al.* [11] reported that intrarenal elasticity values vary with tissue anisotropy and with vascular and urinary pressure level.

The remaining 8 biopsied patients had changes due to immunosuppression therapy, diabetic nephropathy, cast nephropathy or chronic rejection process. All of them had elastography value of  $> 8.23\text{kPa}$ .

Study by Nitin P Ghonge *et al.* [7] had the mean renal allograft parenchymal stiffness measured with shear-wave sonoelastography  $12.25 \text{ kPa} \pm 6.72$  (range,  $3.94-32.98 \text{ kPa}$ ). The mean parenchymal stiffness values in stable allograft, acute allograft dysfunction, and chronic allograft dysfunction were  $8.51 \text{ kPa} \pm 2.44$ ,  $11.06 \text{ kPa} \pm 2.91$ , and  $24.50 \text{ kPa} \pm 4.49$ , respectively.

There were a few limitation to this study. Small sample size (40 patients) is the major set back for this study. Lack of histopathology correlation makes it a subjective study. A single time serum creatinine level was taken to classify patients into stable and unstable graft function groups. Further division into acute and chronic dysfunction needs serial evaluation of serum creatinine, at least for more than 3 months.

Role of body mass index, donor age, type of transplant (live or cadaveric), skin to allograft distance and time since transplant not considered.

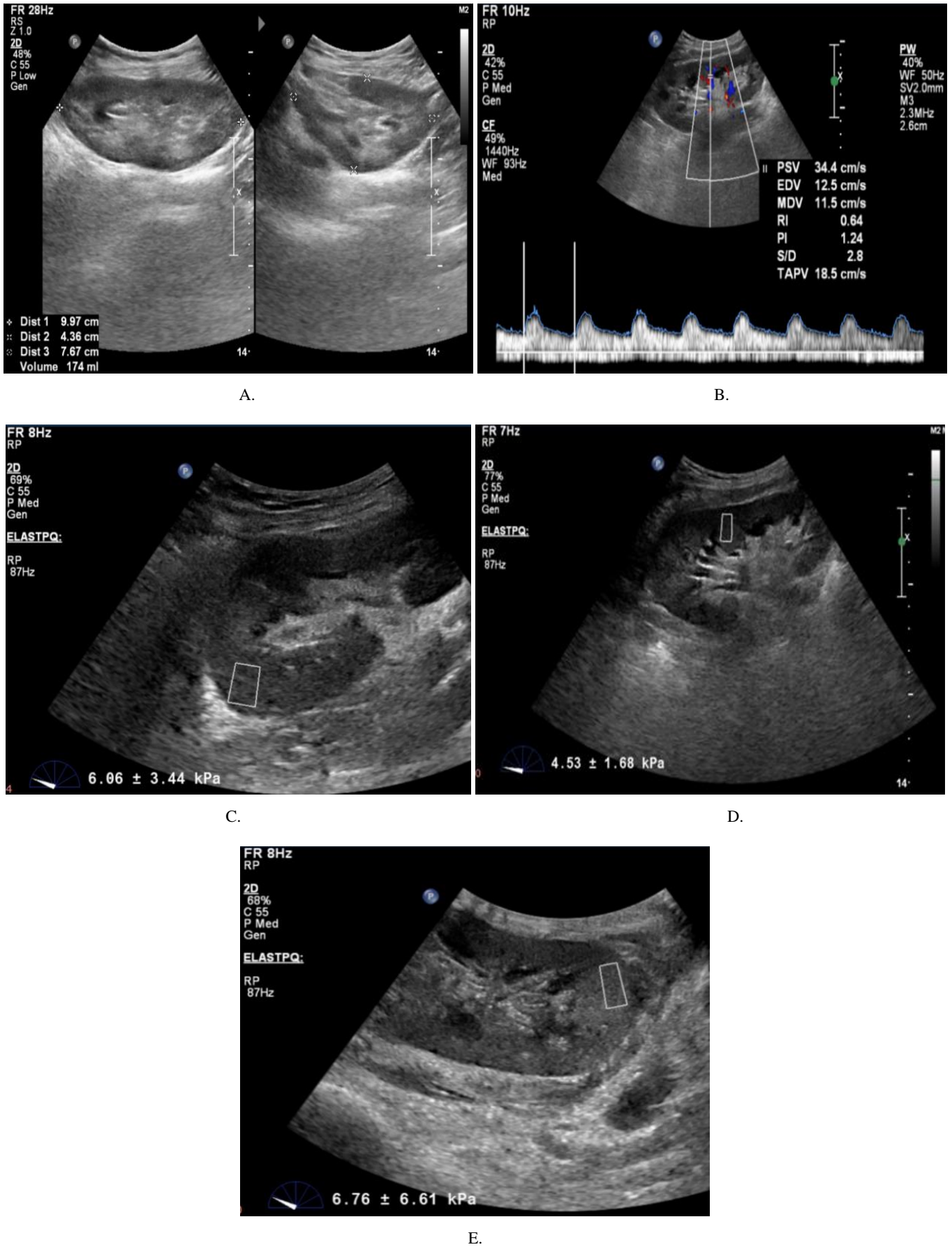
We recommend future study with a large sample size and long term follow up of the serum creatinine, eGFR with histopathology correlation that would have yield a better result.

## 5. Tables and figures

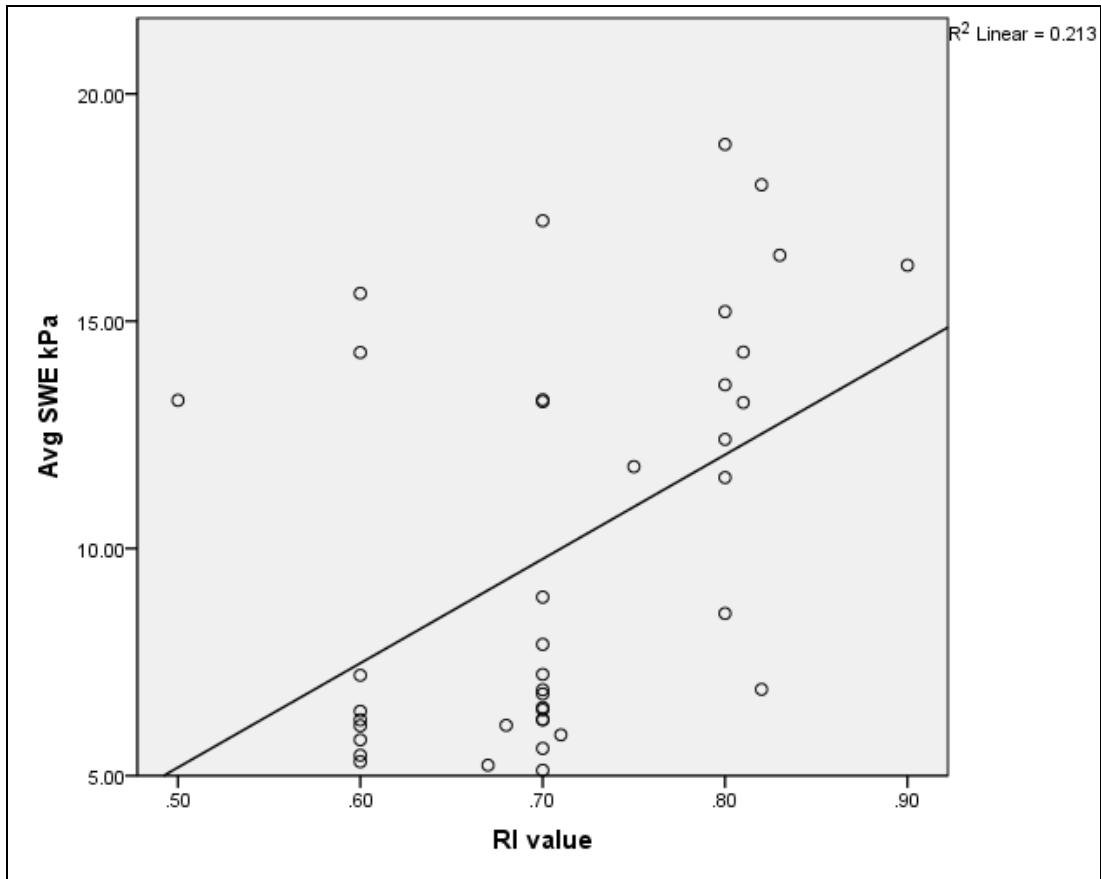
**Table 1:** Shear wave elastography value in 2 group of patients

	SWE value <8.23kPa	SWE value > 8.23kPa
Serum Creatinine $<1.2\text{mg/dL}$	13	-
Serum Creatinine $>1.2\text{mg/dL}$	8	19
Total	21	19

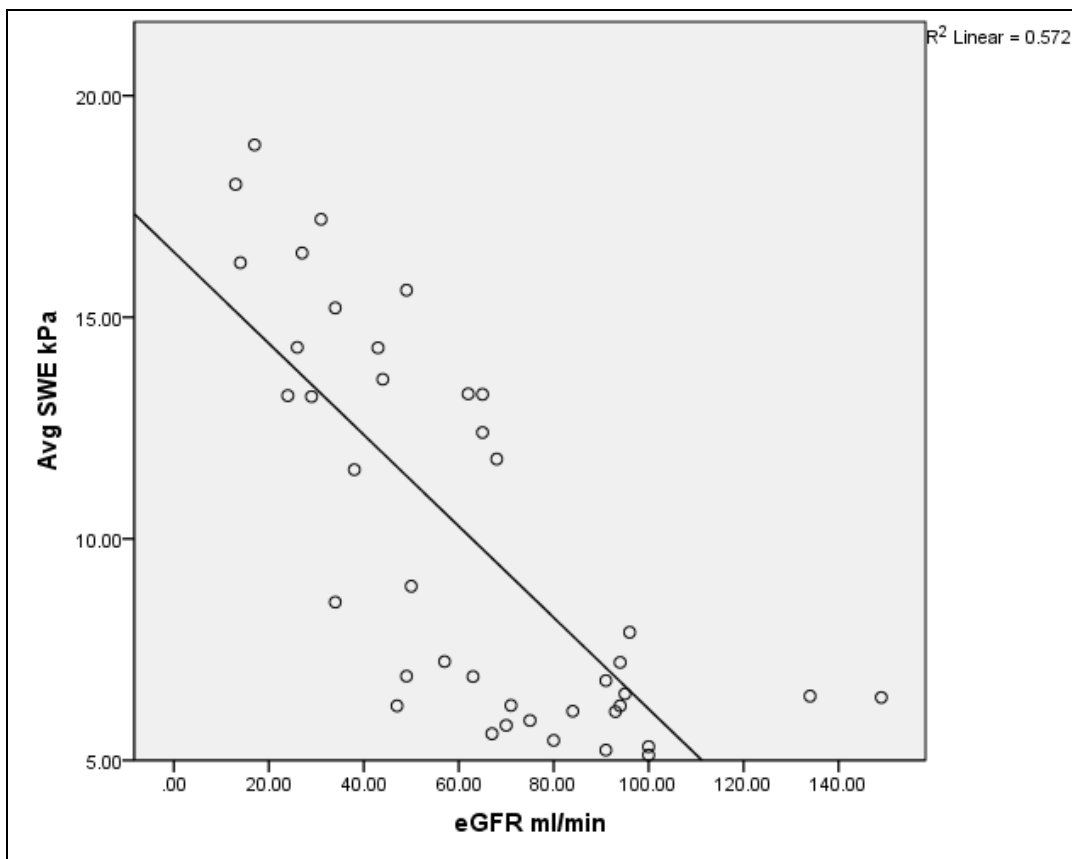
SWE: shear wave elastography value



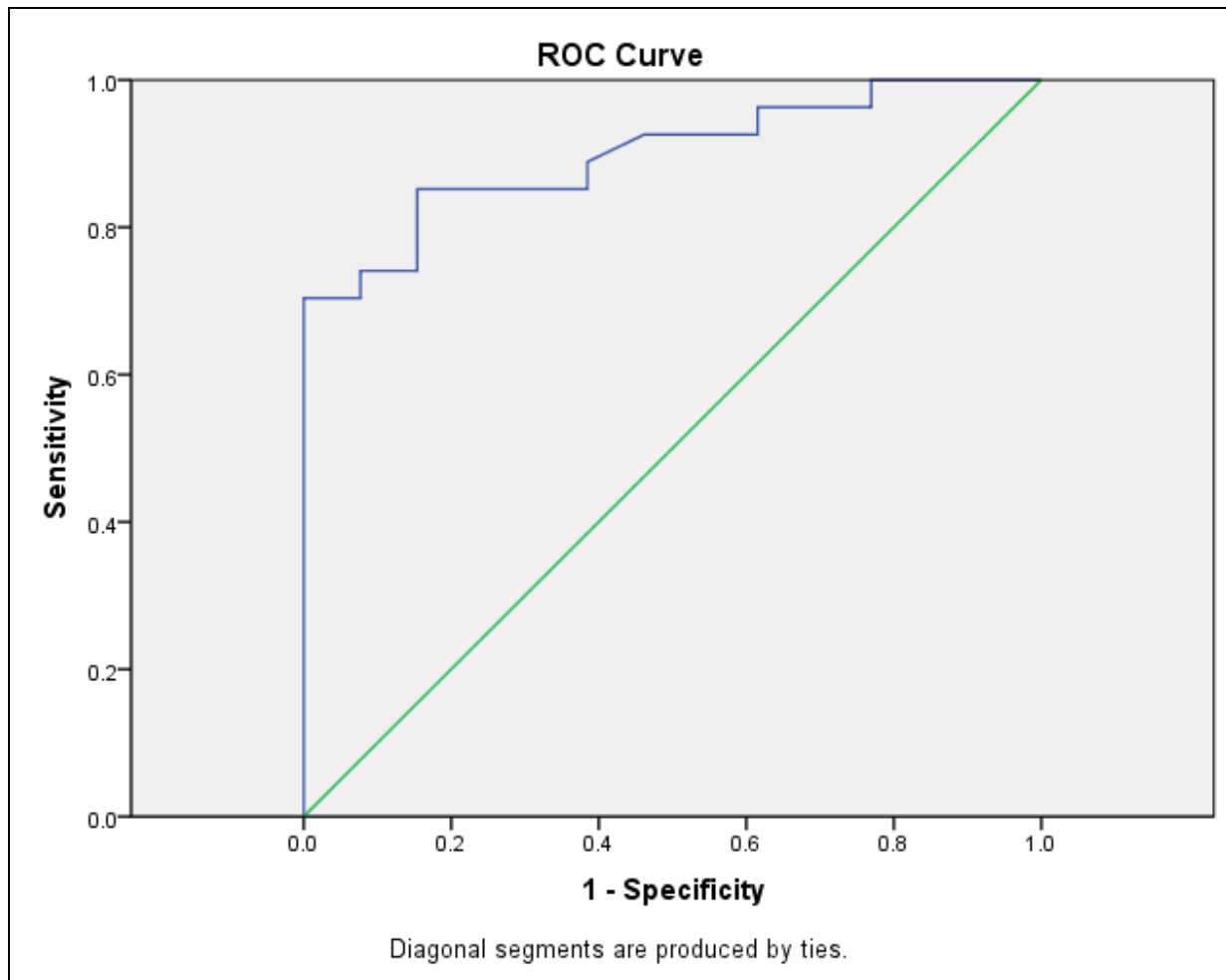
**Fig 1A-E:** In a 57 years old male patient with stable allograft function. (A)Shows a overall B-mode examination with Doppler RI value from the mid pole(B) and SWE value from upper (C), mid (D) and lower poles (E) respectively.



**Fig 2:** Graph shows direct correlation of shear-wave sonoelastography allograft parenchymal stiffness with resistive index (Pearson  $r = 0.46$ ;  $P, .003$ )



**Fig 3:** Graph shows inverse correlation of shear-wave sonoelastography allograft parenchymal stiffness with eGFR (Pearson  $r = -0.75$ ;  $P, .000$ )



**Fig 4:** Graph shows receiver operating characteristic curve of parenchymal stiffness in differentiation of stable allograft from allograft dysfunction (area under the curve = 0.899; 95% confidence interval: 0.80, 0.99;  $P = .000$ ). This suggests that shear-wave sonoelastography-based parenchymal stiffness enabled differentiation of stable allograft from allograft dysfunction. Sensitivity of 70.04% and specificity of 100% at cut-off threshold value of 8.23kPa for differentiating stable allograft from allograft dysfunction.

## 6. Conclusion

This study showed a direct correlation between Resistivity index and elastography value; inverse correlation between estimated glomerular filtration rate and elastography value making shear wave elastography a screening procedure that can be added to the routine sonography examination.

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