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RESEARCH

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Renal resistive index as a marker of histopathological damage in diabetic and non-diabetic chronic kidney disease

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Abstract

Background Chronic kidney disease is a worldwide public health problem with diabetes being the leading cause. Renal resistive index derived by Duplex Doppler sonography, has been in use clinically to examine intrarenal hemodynamic abnormalities. However, renal biopsy remains the gold standard for the evaluation of intrarenal damage. In this study we correlated the renal resistive index in diabetic and non-diabetic kidney disease patients with the established parameters of renal dysfunction i.e. histopathological changes.

Results The conducted study was a cross-sectional comparative study on 114 patients (58 diabetic and 56 non-diabetic patients) over a period of 18 months. Evaluated histopathological indices and renal resistive index had a statistically significant positive correlation (glomerulosclerosis, arterial damage and tubulo-interstitial damage scores) in both diabetic and non-diabetic patients. The highest correlation was observed with tubulo-interstitial score in our study.

Conclusions Renal resistive index could be considered a marker of histological damage in both diabetic and non-diabetic kidney disease. Inclusion of resistive index in the routine diagnostic protocol of chronic kidney disease can help in the accurate assessment of intrarenal damage. Hence, it is of utmost importance as a radiologist to determine resistive index in chronic kidney disease patients and guide the clinicians for efficient management.

Keywords Chronic kidney disease, Renal resistive index, Histopathological indices

Background

Chronic Kidney Disease, which is characterised by kidney damage lasting longer than three months with or without a decline in GFR or a decline in GFR lasting longer than three months with or without kidney damage, is a major global public health issue [1]. Diabetes is considered to be the leading cause for CKD, with diabetic nephropathy occuring in 30–40% of people with diabetes [2]. Prevalence of diabetic kidney disease is raising continuously with India being in one of the top positions [3]. Histopathological evaluation through biopsy remains the gold standard for the evaluation of intra renal damage, which is invasive, expensive and is subject to sampling error. Therefore, there is a critical need to develop non-invasive, cheaper and faster reproducible alternative to detect intra renal damage (Tables 1, 2, 3).

Duplex Doppler Sonography has been in use clinically to examine intra renal hemodynamic abnormalities [4]. Renal Resistive Index (RRI) derived by this method is an excellent marker for demonstrating dynamic or structural changes of intra renal vessels. Even though there

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Table 1 Glomerulosclerosis scores (0–4)

GS score	Findings
0	Normal
1	Mesangial matrix expansion or mild sclerosis < 25%
2	Moderate sclerosis ~ 26–50%
3	Severe sclerosis ~ 51–75%
4	Severe sclerosis ~ > 75%

Table 2 Arterial damage scores (0–4)

AT score	Findings
0	Normal
1	Medial thickening
2	Segmental hyalinosis
3	Global hyalinosis
4	Luminal occlusion with thrombus or infiltrating cells or fibrinoid necrosis or intimal thickening

Table 3 Tubulo-interstitial damage scores (0–4)

TI score	Findings
0	Normal
1	TI damage < 25%
2	TI damage ~ 26–50%
3	TI damage ~ 51–75%
4	TI damage ~ > 75%

are several studies that show RRI as an independent predictor of declining renal function, only few has shown the association between RRI and CKD with or without diabetes.

Hence in this study, we aim to evaluate the intra renal hemodynamic abnormalities with RRI using Doppler sonography in diabetic and non-diabetic kidney disease patients, and correlate it with the established parameter of renal dysfunction i.e. histopathological changes.

Methods

An 18-month cross-sectional comparison study was conducted on 114 individuals (58 diabetic and 56 non-diabetic patients) at the Department of Radiology, JSS Hospital, Mysuru. All CKD patients (with and without diabetes) who had undergone histological examination and were sent to the radiology department for ultrasound evaluation of abdomen were included in the inclusion criteria. Ages under 18, patients with renal artery stenosis or urinary tract obstruction, renal transplant recipients, and patients receiving renal replacement therapy were all excluded from the study.

After acquiring the patients' informed consent and pertinent clinical history, they were subjected to renal Doppler interrogation of inter lobar arteries by colour and spectral Doppler using two different ultrasound machines made by Philips (Philips Healthcare, Best, Netherlands): the IU22 and HD 11XE, both equipped with a 1–5 MHz convex probe. Both the kidneys in a supine patient were evaluated and inter lobar arteries were visualised using colour Doppler along the border of medullary pyramids. Pulsed Doppler mode was used to obtain the sample volumes, by placing the cursor at the mid portion of the interlobar arteries (2–4 mm of Doppler sample volume and < 60 degrees of angle of insonation) at three poles (upper, middle and lower) in each kidney. It gave the quantitative measurements of velocities and resistance parameters. The Renal Resistive Index was calculated as the mean of both the kidneys. The difficulty encountered during performing renal Doppler was overcome by breath-hold techniques.

The renal biopsy samples were examined for the severity of glomerulosclerosis (GS), arterial damage (AT), and tubulo-interstitial damage (TI) based on five-level scoring systems. GS and AT scores were evaluated in periodic acid-Schiff (PAS) stained sections.

Azan- or periodic acid-methenamine silver (PAM) stained sections were used to assess TI score.

Patient's medical records were examined for parameters like age & serum creatinine, and used for the calculation of eGFR.

Statistical analysis

The sample size was obtained by the formula $n = ((Z\alpha + Z\beta)^2 \times S^2 \times 2)/d^2$, where $Z\alpha = Z$ value for α error, $Z\beta = Z$ value for β error, $S =$ Common standard deviation between the two groups, $d =$ Clinically meaningful difference. Assuming at least a RRI difference of 0.03 between diabetic and non-diabetic kidney disease patients with an expected standard deviation of 0.08 in each group, with a confidence level of 95%, α level of 5% and a power of 80%, a sample size of 55 in each diabetic and non-diabetic groups were at least needed to be studied.

Lab values of RFT were obtained and eGFR calculated by the CKD-EPI formula:

$$\text{GFR (mL/min)} = 141 \times \min(\text{S Cr}/K, 1)\alpha \times \max(\text{S Cr}/K, 1) - 1.209 \times 0.993^{\text{Age}} \times 1.018(\text{if female}) \times 1.159(\text{if black})$$

where, $K = 0.7$ if female, 0.9 if male; $\alpha = -0.329$ if female, −0.411 if male; min = The minimum of S Cr/K or 1; max = The maximum of S Cr/K or 1.

The data were entered into MS Excel followed by analysis using SPSS version 22 licensed to the institution. The

correlation of RRI and histopathological changes in diabetic and non-diabetic kidney disease patients were calculated using Pearson's correlation coefficient. A p value < 0.05 will be considered statistically significant.

Results

In our study, about 62% (71 cases) were males and the rest were females. Majority of patients were in the age group of 31–45 years (39%). The mean age for diabetic patients (51 years) was significantly higher compared to non-diabetic patients (35 years) with p value of 0.001.

The histopathological specimens of both diabetic and non-diabetic kidneys were scored based on glomerulosclerosis, arterial damage and tubulo-interstitial damage. Diabetes was significantly predominant in patients with higher scores (≥ 3), with lower scores (< 3) predominantly in non-diabetic patients (GS-$p = 0.003$, AT-$p = 0.003$, TI-$p = 0.011$) (Fig. 1).

Renal resistive index showed remarkable positive correlation with all histopathological indices (GS, AT and TI scores) in both diabetic and non-diabetic patients, with highest correlation observed with tubulo-interstitial score (Diabetic patients GS- r value = 0.679, AT- r value = 0.398, TI- r value = 0.709) (Non-diabetic patients GS- r value = 0.467, AT- r value = 0.426, TI- r value = 0.563) (Figs. 2, 3).

Whereas, the mean serum creatinine levels were remarkably higher in diabetic patients compared to non-diabetic ($p = 0.007$). A significant difference in mean eGFR was noted between the two groups, with a higher mean value in non-diabetic group ($p = 0.001$).

Also diabetic patients showed a significantly higher renal resistive index values (mean—0.72) than non-diabetic patients (mean—0.65) ($p = 0.001$). There was a notable negative correlation between renal resistive index and eGFR, signifying that RRI progressively increased from lower to higher stages of CKD.

Discussion

Numerous pathophysiologic processes are involved in chronic kidney disease, and its frequency and incidence are rising. It needs a thorough understanding of the available efficacious diagnostic techniques and effective treatment modalities for proper patient management.

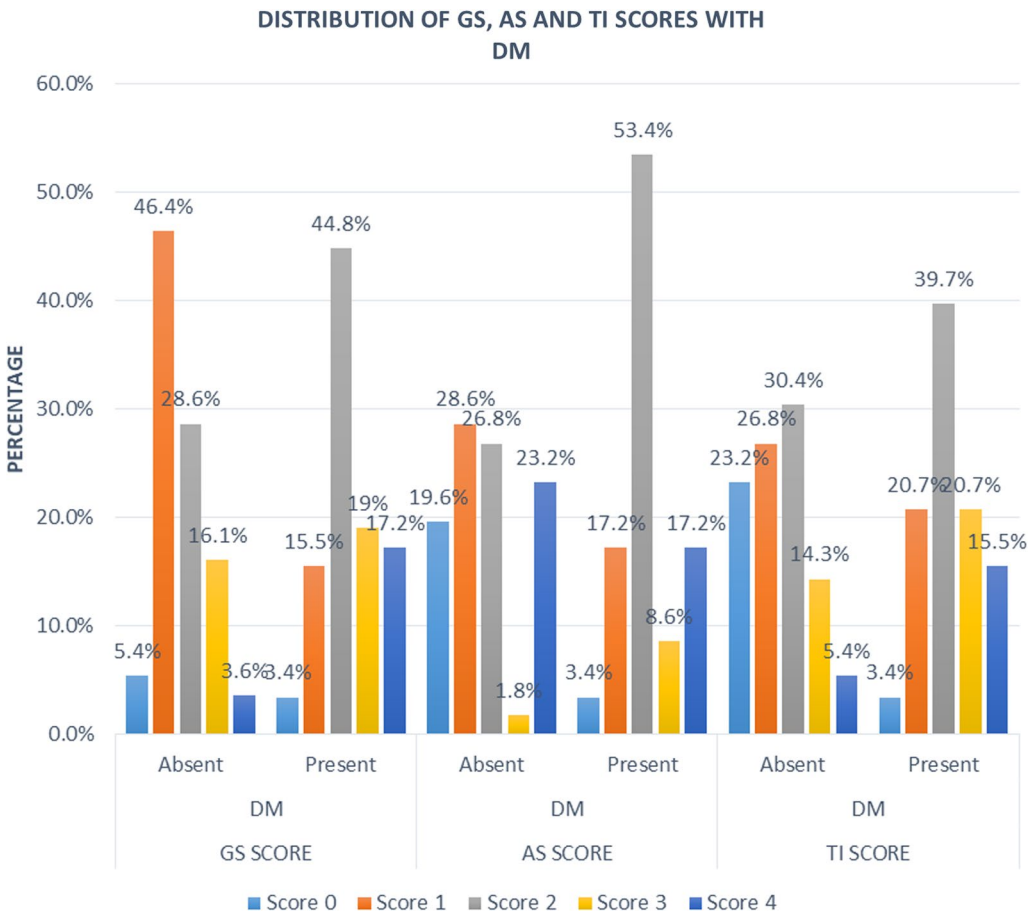

Fig. 1 Bar chart illustrating distribution of diabetic and non-diabetic CKD patients based on histopathological scores (GS, AT and TI)

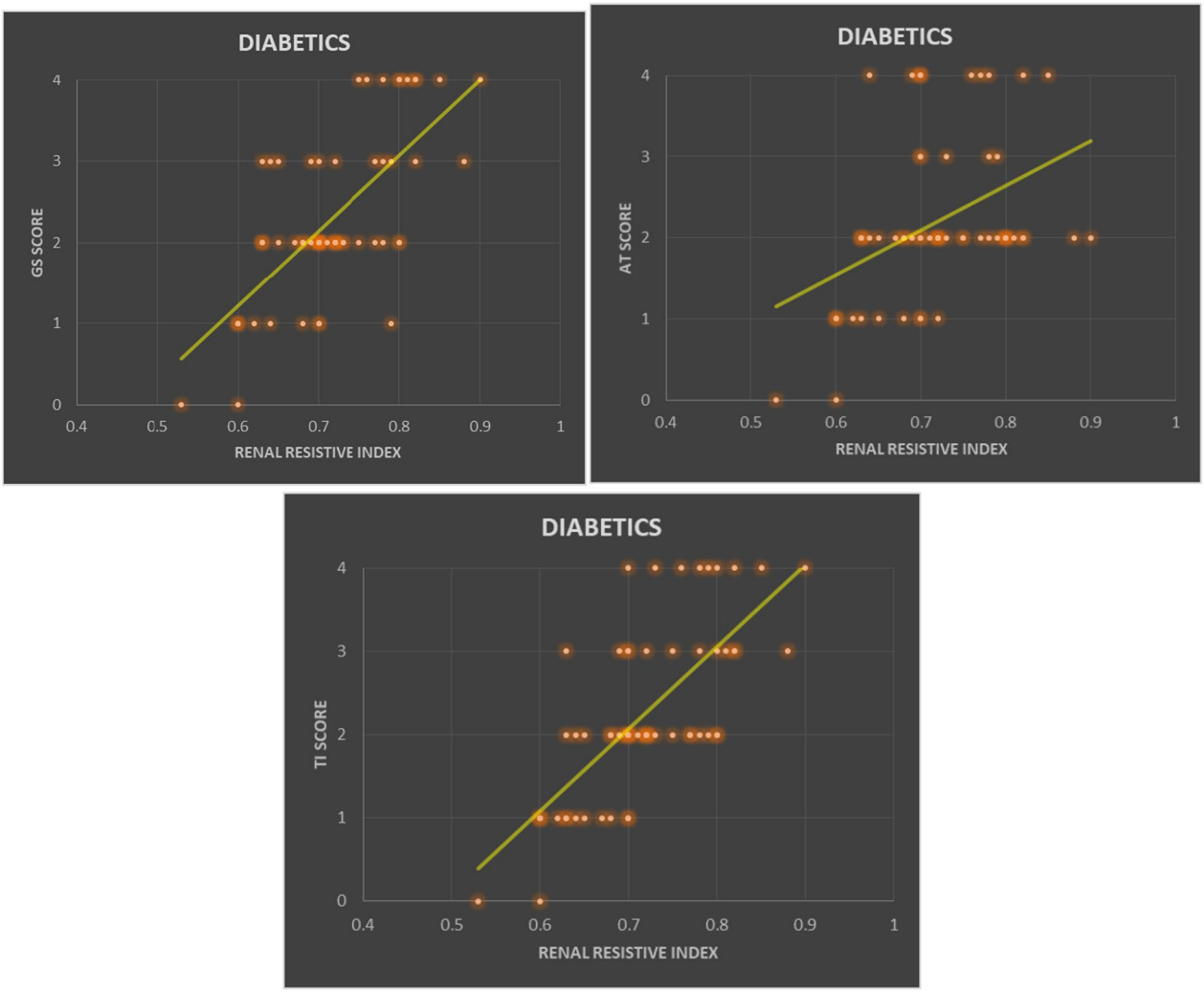

Fig. 2 Scatter diagram illustrating correlation of RRI and GS, AT & TI scores in diabetic patients

Diabetic nephropathy is the most common cause of CKD causing tremendous burden worldwide.

Mogensen et al. studied the natural progression of diabetic nephropathy, who following extensive work on diabetic subjects, identified five stages of DN [5]. At the early stages, diabetic kidney disease is characterized by a decrease in the resistance of the afferent and efferent glomerular arterioles leading to increased renal perfusion and glomerular hyperfiltration. Ultimately it leads to increased permeability of renal albumin and extracellular matrix accumulation, which results in increasing proteinuria, glomerulosclerosis and tubulo-interstitial fibrosis [6]. As a result there is a reduction in the number and area of post glomerular capillaries. Further reduction in the intrarenal vessel area could be caused by renal scarring, which in turn may be responsible for an increased intrarenal vascular resistance. In our study, diabetic patients had higher histopathological scores than non-diabetic patients, an indirect sign of how diabetes accelerates glomerular, interstitial, and vascular damage in people, causing end-stage chronic kidney disease to develop early.

Literature exhibits very few studies that correlated renal resistive index with histopathological parameters. One of them, Hanamura et al. [7] had shown correlation of RRI with all histological indices (glomerulosclerosis, arteriosclerosis and tubulo-interstitial damage), with highest correlation observed with tubulo-interstitial lesions. Whereas Ikee et al. [8] reported that arteriosclerosis showed the best association with raised RRI.

In the present study we found that RRI is related with glomerulosclerosis, arterial damage and tubulo-interstitial damage, with maximum correlation between RRI and tubulo-interstitial lesions (Figs. 4, 5, 6, 7). Early stages of CKD is characterised by primary glomerular involvement [9]. Whereas interstitial fibrosis and tubular atrophy are

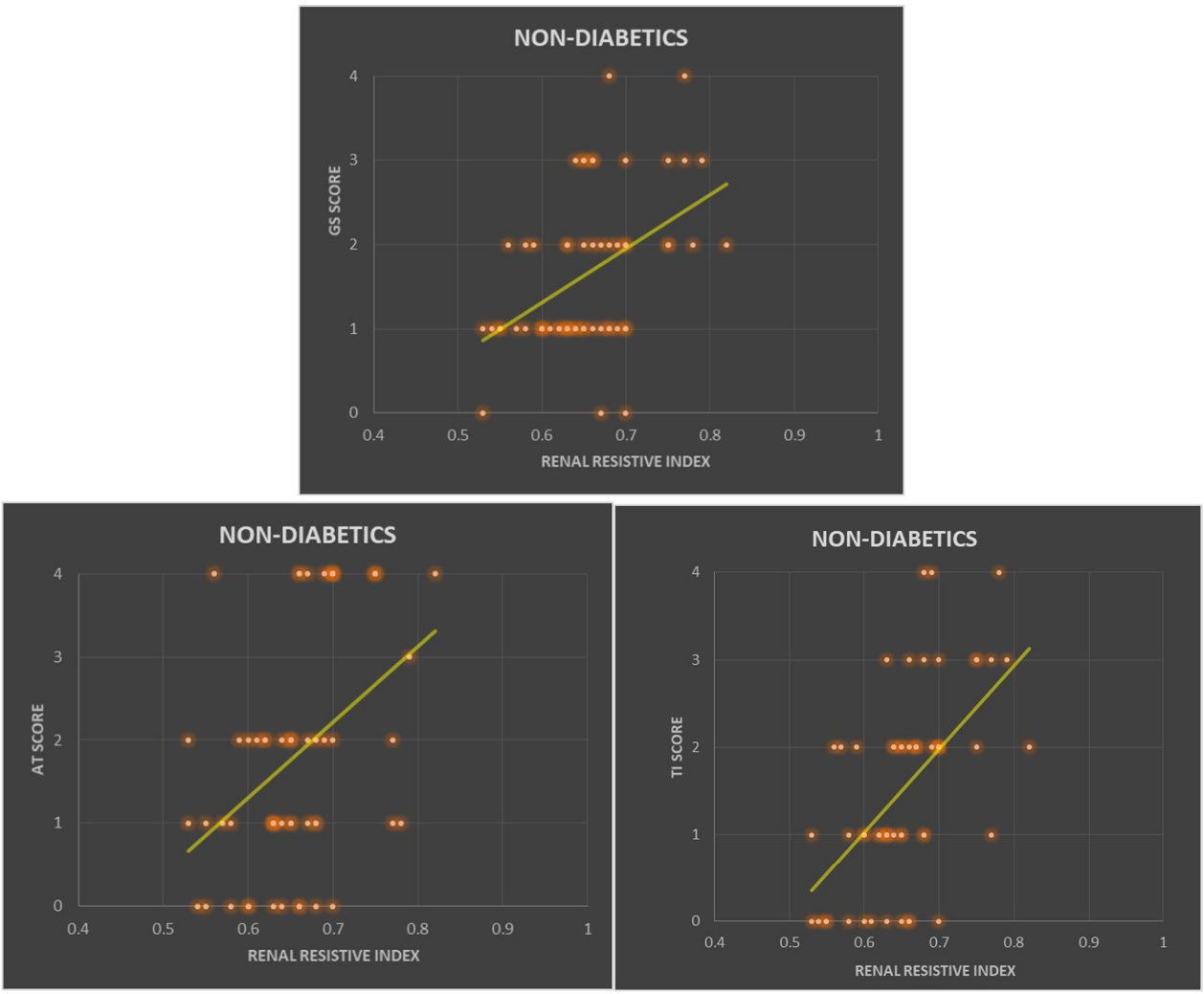

Fig. 3 Scatter diagram illustrating correlation of RRI and GS, AT & TI scores in non-diabetic patients

commonly seen in advanced kidney injuries. Increased resistance to cortical blood flow is witnessed due to alterations in post-glomerular vessels by interstitial fibrosis leading to reduction in glomerular perfusion and function. While this maybe the pathophysiology, the precise process by which tubulo-interstitial injury results in an increase in RRI is still unknown.

Few studies were done in the past to find a renal threshold for RRI beyond which renal damage could be suspected. Sugiura et al. [10] proved that a RRI > 0.7 is an independent predictor of risk of worsening renal function, in patients with mild to moderate diabetic nephropathy. However our study showed several CKD subjects who had RRI value less than 0.7, predominantly in the earlier stages. This shows the significance of serial follow up and prospective continuous evaluation of the CKD patients using renal Doppler after a baseline RRI for predicting the accurate outcome.

Renal biopsy has remained the gold standard for detection of alterations in diseased kidney since ages. It is capable of providing a complete data on the glomerular, vascular and interstitial damage within the kidney. Also it has the ability to predict the etiopathogenesis of kidney disease i.e. whether diabetic or non-diabetic cause.

While it was shown in our study that increasing RRI might predict increased intrarenal histopathological damage, it was unable to provide all the information regarding the severity of the injury and its etiopathogenesis. Hence, biopsy will continue to remain the prime modality for complete evaluation of kidney disease patients and other imaging or biochemical parameters would remain an adjunct tool in evaluation of chronic kidney disease.

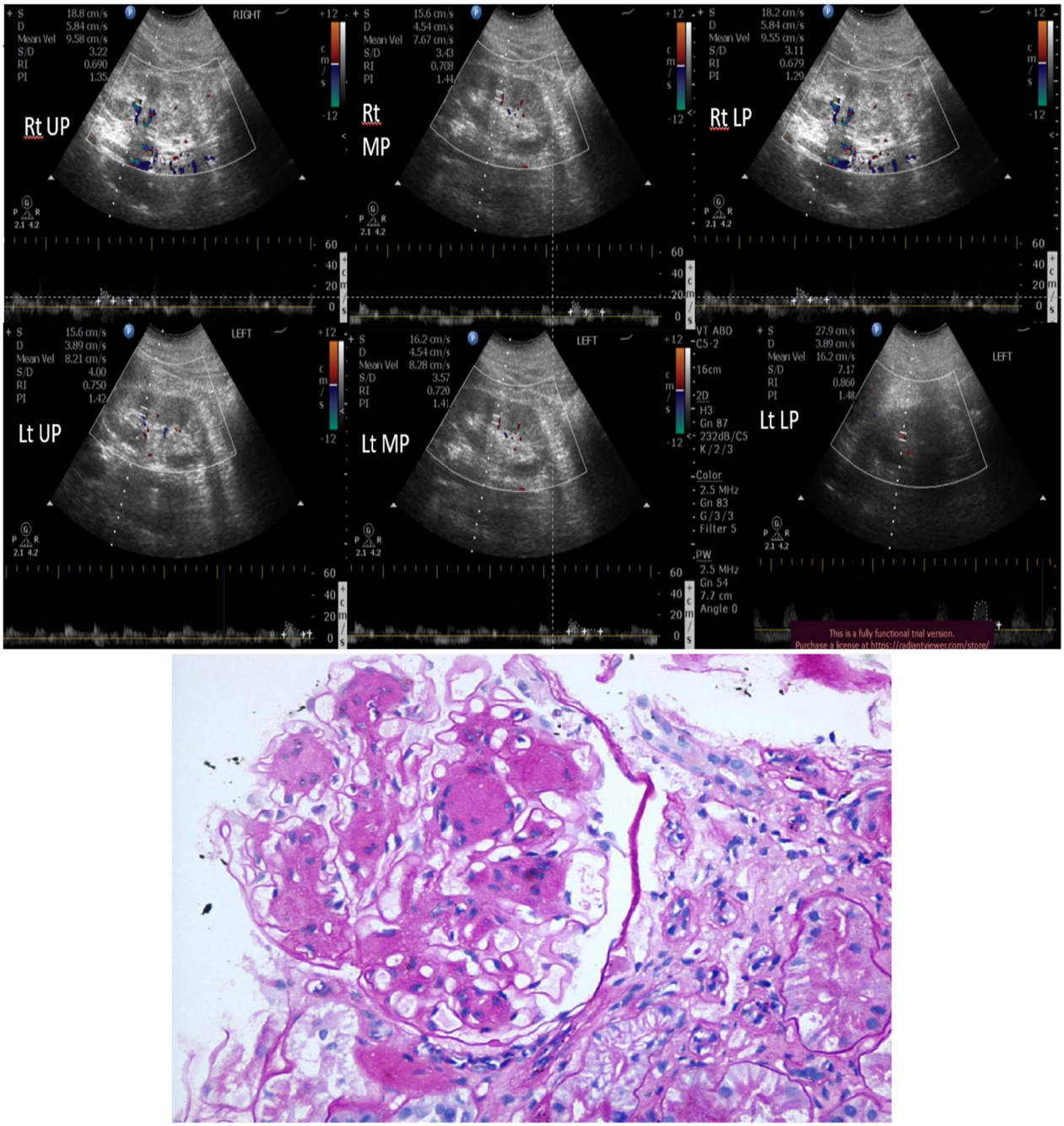

Fig. 4 52 year old diabetic male with stage IV CKD average RRI = 0.73 and Histopathology showed increase in mesangial matrix and cells. Capillary loops were patent with thick single contoured basement membrane. KW nodules were seen. Intimal fibroplasia and medial hyperplasia of large arteries noted with intimal thickening more than medial thickening. Tubular atrophy and interstitial fibrosis was seen in ~ 55–60% of the sampled area. Findings were consistent with Class IV diabetic nephropathy (GS 3, AT 4, TI 3)

Limitations

Confounding factors such as age, gender, muscle mass and BMI were not matched in the study. Baseline RRI values were not taken for the patients at initial stages of CKD. Also a prospective continuous evaluation with serial RRI values would have helped more in predicting the outcome.

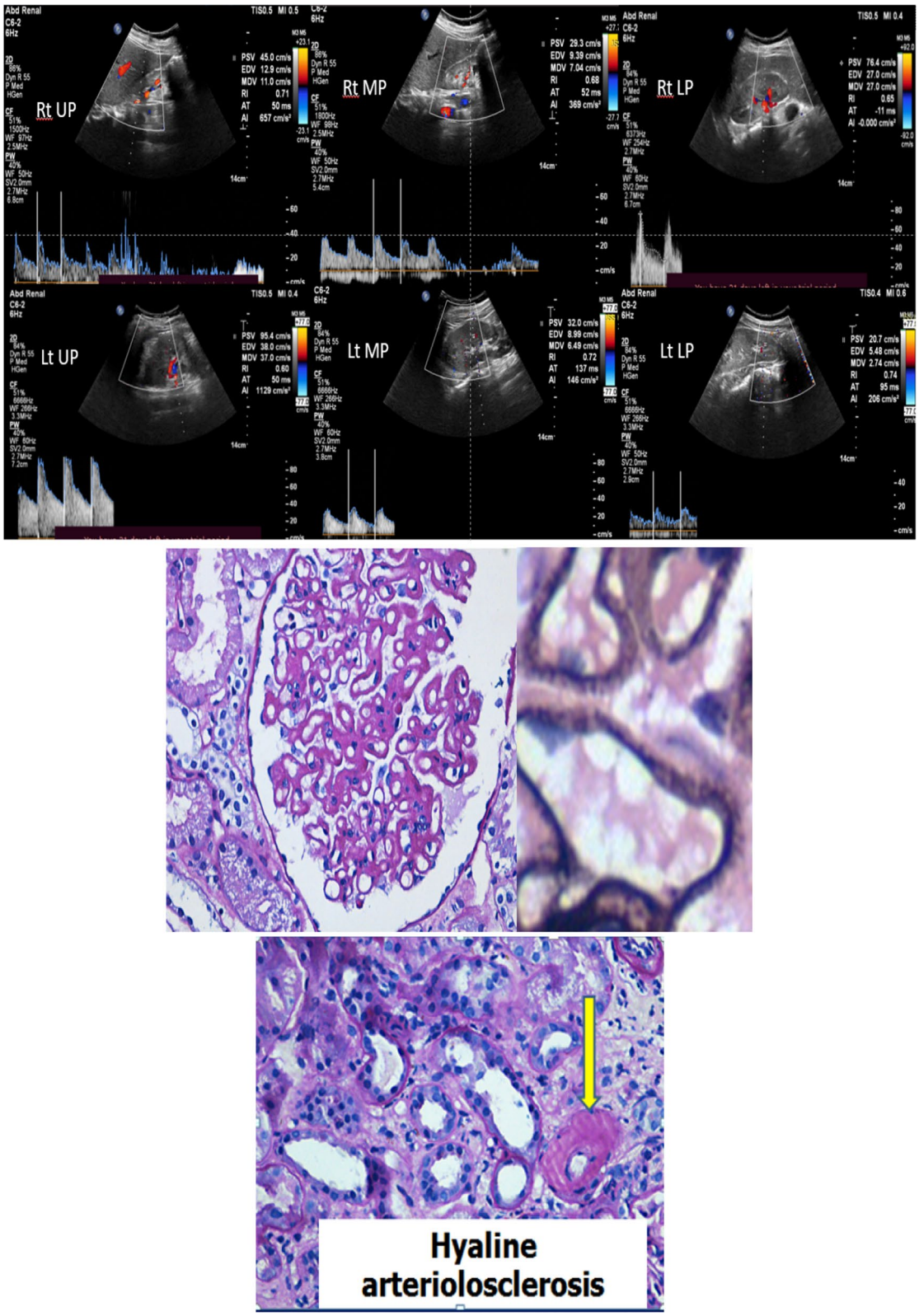

Fig. 5 34 year old non-diabetic female with stage IV CKD average RRI = 0.68 and Histopathology showed diffuse increase in mesangial matrix and mesangial cellularity. Segmental sclerosis noted in 30% of the glomeruli. Moderate hyaline arteriosclerosis noted with ~ 30–35% tubular atrophy—findings consistent with Membranous glomerulonephritis (GS 2, AT 2, TI 2)

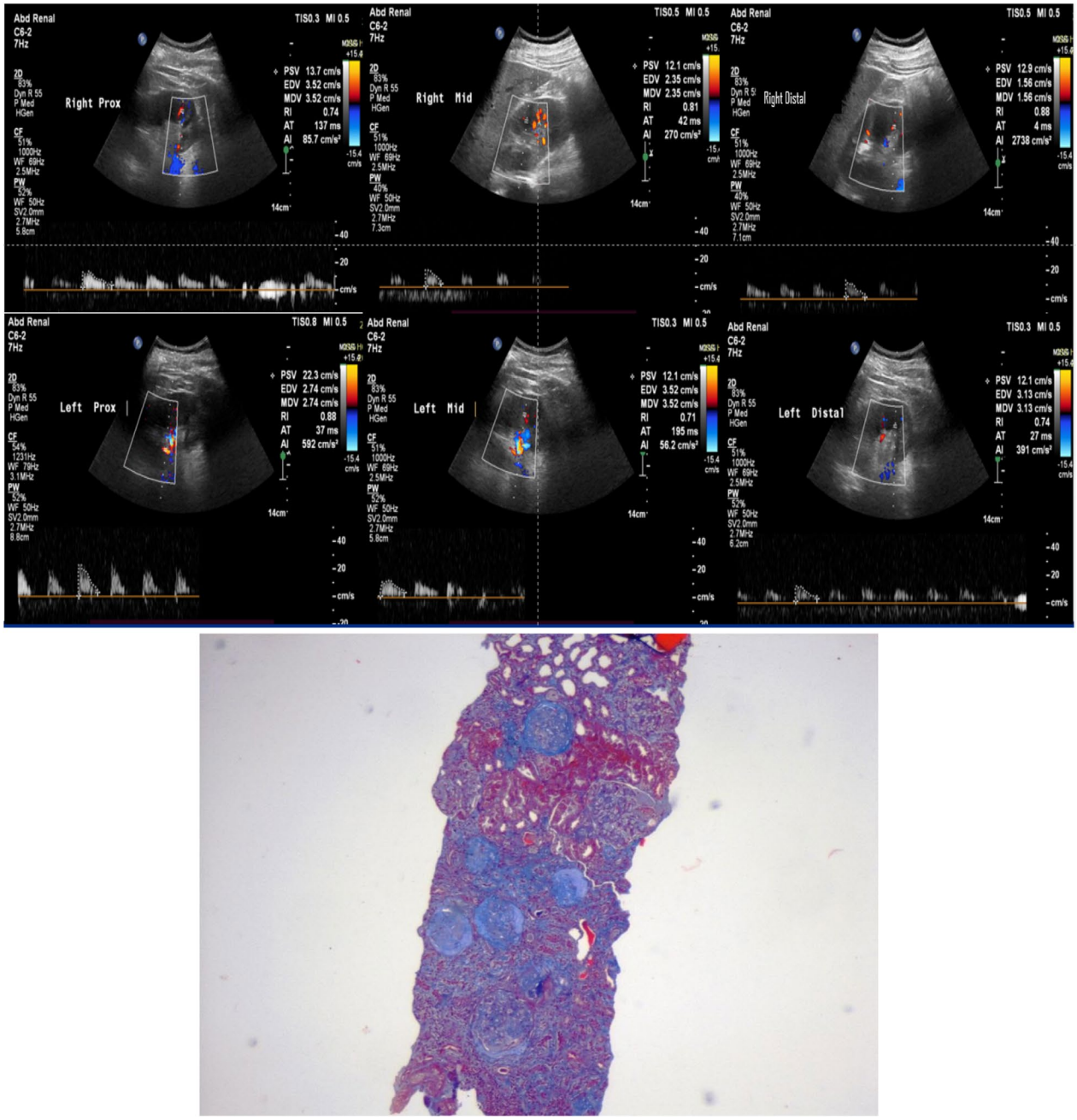

Fig. 6 32 year old diabetic female with stage V CKD average RRI = 0.79 and Histopathology showed Histopathology showed increase in mesangial matrix and cells with global sclerosis in > 75% of glomeruli. KW nodules were seen. Intimal fibroplasia and medial hyperplasia of large arteries noted with intimal thickening more than medial thickening. Tubular atrophy and interstitial fibrosis was seen in > 75% of the sampled area. Findings were consistent with Class V diabetic nephropathy (GS 4, AT 4, TI 4)

Conclusions

Renal biopsy will remain the prime modality to assess the complete pathology and alterations of diseased kidney. Correlation of RRI with extent of histological damage indicates that RRI can be used as an adjunct tool, and is a good marker of renal function and histological damage in both diabetic and non-diabetic kidney disease. Additionally, it was also observed that a consecutive increase in RRI, than a single value, seems to be a better indicator of severity of injury in chronic kidney disease.

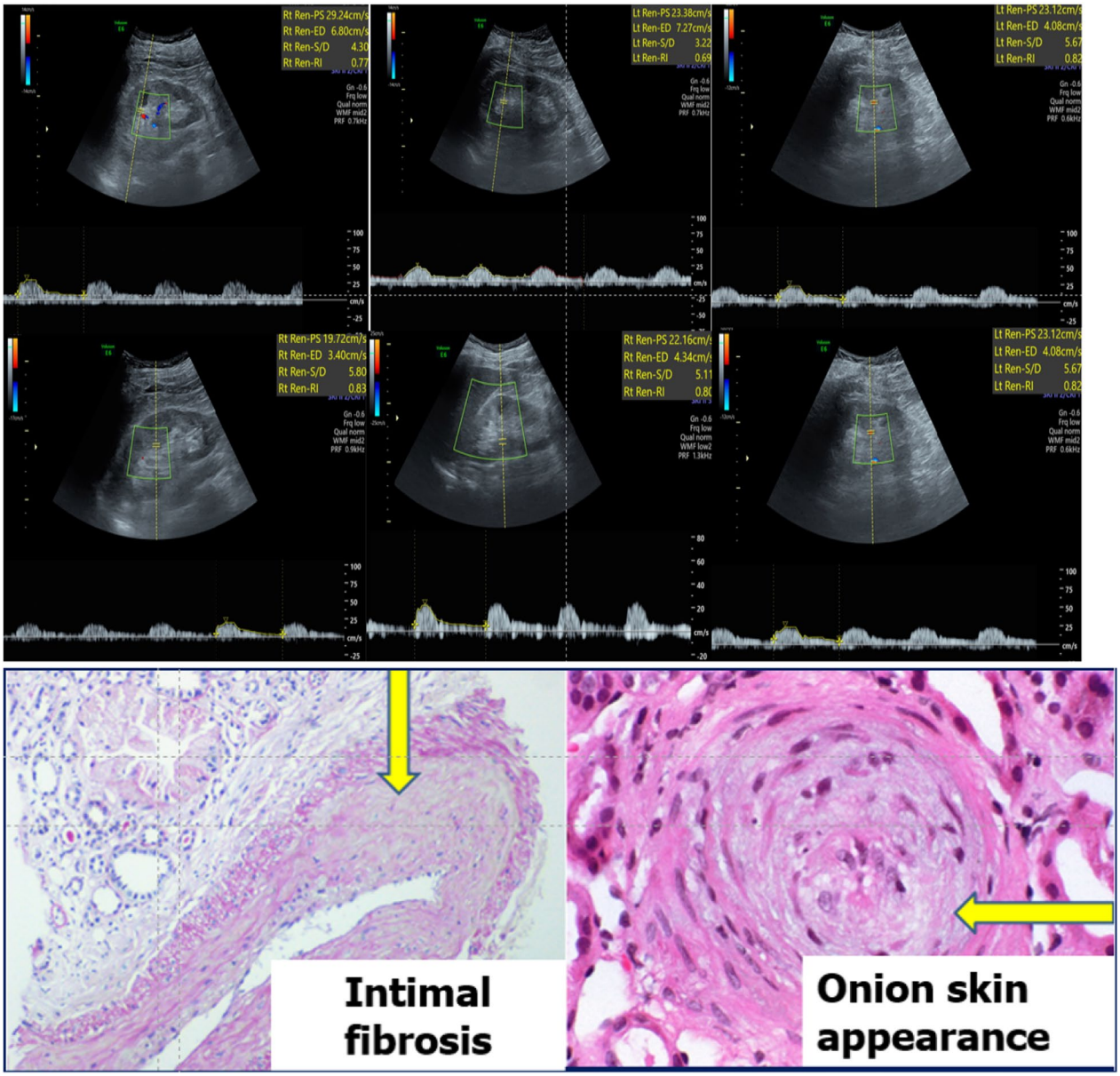

Fig. 7 51 year old non-diabetic male with stage V CKD average RRI = 0.78 and Histopathology showed sclerosis of ~ 60–65% of visualized glomeruli with wrinkling of basement membrane. Tunica intima thickening noted in the vessels with onion-skin appearance. Tubular atrophy and interstitial fibrosis seen in 30–35% of the sampled cortical area—Findings are consistent with hypertensive nephrosclerosis (GS 3, AT 4, TI 2)

Abbreviations

GFR	Glomerular filtration rate
CKD	Chronic kidney disease
USG	Ultrasonography
RRI	Renal resistive index
GS	Glomerulosclerosis
AT	Arterial damage
TI	Tubulo-interstitial damage

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Author contributions
Dr T.K.C.—Study conception and design, draft manuscript preparation. Dr. S.K.D.—Study conception and design, analysis and interpretation of data. Supervision of the project. Dr. M.S.S.—Study conception and design, analysis and interpretation of data. Supervision of the project. Dr. S.S.—Study conception and design, analysis and interpretation of data. Supervision of the project. Dr. B.B.—Study conception and design, draft manuscript preparation. All authors discussed the case report and contributed to the final manuscript.

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Availability of data and materials
The datasets generated and/or analysed during the current study are not publicly available due to privacy of the study participant.

Declarations

Ethics approval and consent to participate
Approval was waived off by the Ethics committee of JSS Academy of Higher Education and Research, Mysuru, India for cross sectional study and written informed consent for publication was obtained from the patient. Only anonymized data and images were used.

Consent for publication
Written informed consent was obtained from the patient for the publication and only anonymized data and images were used.

Competing interests
Not applicable.

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