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***Original Article***

# Which Better Determines the Renal Function and Glomerular Filtration Rate: Renal Parenchymal Thickness or Renal Resistive Index?

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**ABSTRACT.** Resistive index (RI) could provide more useful diagnostic and prognostic information for kidney disease than parenchymal thickness (PT) only. The aims of this study were to find the association between PT, glomerular filtration rate (GFR), and RI and their determination of renal function. B-mode and Doppler ultrasonography and standard biochemical laboratory testing (urea and creatinine) were performed among 75 participants (57.1 ± 10.6 years). We measured PT and RI and calculated GFR. The mean and standard deviation were 0.671 ± 0.041, 12.24 ± 1.98 mm, and 86.38 ± 15.96 mL/min/1.73 $m^2$ for RI, PT, and GFR, respectively. The mean RI in two subgroups with PT smaller or greater than 12.5 mm was $RI_1$ = 0.692 ± 0.038 or $RI_2$ = 0.648 ± 0.03 ($P$ <0.0001). Strong inverse correlation between RI (y) and PT (x) presented by the linear regression equation: y = 0.744 + (−0.005932 x). By multiple regression, we show GFR and PT as predictors for increasing of RI ($R^2$ = 0.2063, βst = −0.0009176, $P$ = 0.0012 and βst = −0.006003, $P$ = 0.0078), respectively. Renal RI inversely strongly correlates with the PT and GFR. Renal PT and GFR are independent predictors for increasing of RI in general population.

## Introduction

B-mode ultrasound and Doppler ultrasound imaging has also traditionally been used in the assessment of chronic renal disease.[1] B-mode ultrasound is able to give information about echogenicity and thickness of renal parenchyma. The distance between the cortex capsule and the apex of sinus pyramids of the kidney is named renal parenchymal thickness (PT).[2] Hyperechogenicity is a nonspecific finding but a significant one in that it suggests the presence of renal disease but correlates poorly

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with the type of renal disease.[3] Like total renal length, PT gives an indication of the chronicity of renal failure. Some patients with PT ≤1.5 cm still have potential for renal improvement.[4] The irreversible change was associated with a parenchymal thickness <1.0 cm.[1]

In authority of Lerolle et al (2006), Doppler ultrasonography is a noninvasive method widely used in clinical nephrology practice. It detects the advanced changes in blood flow at the microvascular level.

Evaluation of vascular impedance and renal resistive index (RI) at different sites of the renal parenchyma may suggest functional or structural changes within the kidneys which we cannot provide by conventional B-mode ultrasonography. This Doppler parameter (RI) could provide more useful diagnostic and prognostic information than PT only. Color Doppler is essential for assessing the variety of large arterial or venous abnormalities and has been suggested for changes evaluation in addition to intrarenal perfusion due to the renal parenchyma's diseases.[5]

Vascular distensibility is determined by the arteriosclerosis and interstitial fibrosis as pathogenic mechanisms. The RI and other coefficients which are derived by Doppler may be of great importance in measuring vascular stiffness.[6] The RI is commonly used as an index of intrarenal arterial resistance, and it is calculated with the following formula (equation 1):

$$RI = \frac{PSV - EDV}{PSV}$$

or [peak systolic velocity (PSV) − end-diastolic velocity])/PSV.[1]

The aims of this study were as follows: first, to establish both the kidneys' Doppler renal blood flow parameter (RI) and PT in 75 patients from general population, and second, to find the associative connections of those Doppler parameters with renal PT and glomerular filtration rate (GFR).

The aims of this study were as follows: first, to find the association between PT, GFR, and RI in 75 patients from general population, and second, to find the associative connections of those Doppler parameters with functional parameter and their determination of renal function.

## Methods

*Patients*

During one month's period in September 2018, color Doppler ultrasonography evaluations were performed in 75 participants recruited from internal medicine ambulance in Clinical Hospital Dr. Trifun Panovski, stated in Macedonia. Before reporting the patients to Doppler ultrasound RI and PT measurements, some biochemical laboratory testing of urea, creatinine, and GFR (mL/min/1.73 $m^2$) were performed by developing diet modification in renal disease formula which was performed on all the participants.

The group consisted of 46 males and 29 females aged 57.1 ± 10.6 years; their mean body mass index (BMI) was 27.67 ± 4.41 $kg/m^2$. Twenty patients were smokers, 27 were hypertonic, and 16 were diabetics. More detailed demographic and clinical data are presented in Table 1. Informed consent was obtained from all 75 patients, and the Ethics Committee of our institution approved this study.

*Assessment*

We used Doppler ultrasound machine General Electric Logiq Pro 5 (GE Medical Systems – USA: 4855W Electric Avenue, Milwaukee, WI 53215), with abdominal convex array Doppler 3.5 MHz multifrequency ultrasound probe GE 4C-RS (wide-band convex array, 2.5–5.5 MHz). Each patient underwent B-mode and Doppler ultrasound examination of the kidneys (renal parenchyma and renal pelvis) and both renal artery and interlobar velocimetry by three 30-year experienced ultrasonographers. An independent and blinded ultrasonographic review was assessed in all ultrasonography and image analyses, interpretations, and final scoring. Inter-observer reliability was determined using Cohen's kappa coefficient (κ). It was the highest across experience levels for non-alcoholic liver disease detection (κ = 0.953)

and renal RI scoring (κ = 0.947).

After appropriate adjusting and machine settings,[7] renal artery flow was detected and recorded by positioning the sample volume at the renal hilum. Thus, regardless of the resistance, the blood flow was progressively increasing from the hilar arteries toward the more peripheral parenchymal vessels. Recommendation for accurate RI estimation, the two parallel lines (sample volume) should be placed on the arcuate or interlobar arteries located near the medullary pyramids. The measurement technique is shown in Figure 1.[8]

Renal artery flow was detected by positioning the sample volume (white parallel line in yellow rectangular area). In order to maximize waveform size, we used the lowest pulse repetition frequency with aliasing (PRF = 4 KHz) with the lowest wall filter (233 Hz). The baseline (a yellow line in the bottom of the spectral diagram) was deliberately lowered down so that the peak of the spectrum was displayed without aliasing. At least eight reproducible spectral waveforms were preferentially repeated in different anatomic parts of both kidneys (superior, median, and lower), and the mean of all measurements was accepted for the mean RI (including measurement for left and right kidneys). Multiple sampling has been shown to be more effective than a single sampling: by increasing the number of samples, by minimizing the intra-observer variability, and by considering the RI to be a highly reproducible test.

The RI was calculated by machine software according to equation 1. The mean of the renal RI was calculated as an average value of the sum of the left RI and right RI (the mean RI from multiple sampling) divided by two, or

$$RI = \frac{RI\,left + RI\,right}{2} \quad (7).$$

## Statistical Analysis

Statistical analysis was performed using MedCalc for Windows, version 18.11 (MedCalc Software, Ostend, Belgium). Results are expressed as means ± standard deviation (SD) or percentage. Student's *t*-test for unpaired data (Welch's *t*-test and unequal variances *t*-test) was used to compare the results from different PT and RIs. We used Pearson's correlation analysis to find the strength and direction of relationship between two continuous variables. The association between dependent and independent variables was performed by an equation of simple linear regression. The strength and direction of their relationship were expressed by Pearson's *r* coefficient and *P*-value. Backward multiple regression analysis was used to predict the outcome of the response variable.

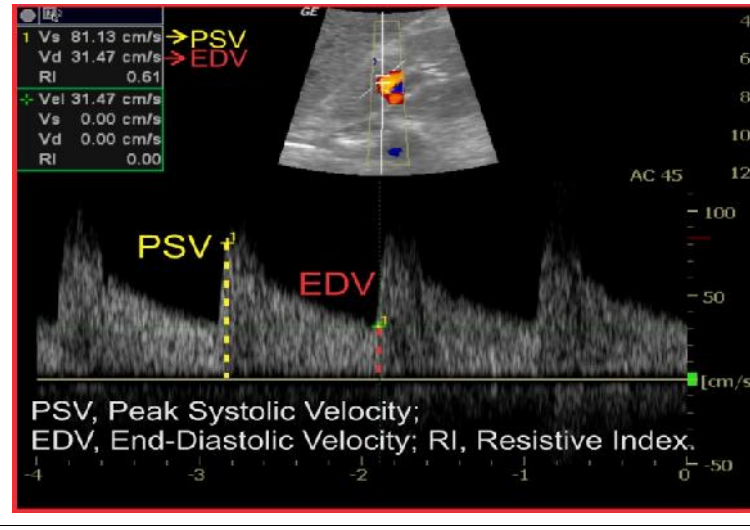


Figure 1. Doppler parameter (PSV, EDV, and RI) measurement technique.

PSV: Peak systolic velocity, EDV: End-diastolic velocity, RI: Resistive index.

Table 1. Demographic and clinical parameters of the studied patients.

| Parameters | Mean | SD | Median | Minimum | Maximum |
|---|---|---|---|---|---|
| Age, year | 57.1 | 10.6 | 55 | 37 | 80 |
| Height, cm | 168.8 | 10.2 | 168 | 150 | 193S |
| Weight, kg | 79.8 | 15.9 | 76 | 50 | 193S |
| BMI, kg/m$^2$ | 27.67 | 4.41S | 27.34 | 20.76 | 120 |
| Hypertension | 27 (20.25%) | | | | 41.52S |
| Diabetes | 16 (12%) | | | | |
| Smoker | 20 (15%) | | | | |
| Urea, mmol/L | 6.7 | 2.1 | 6.7 | 3 | 11.6 |
| Creatinine, µmol/L | 84.9 | 20.1 | 84.5 | 47 | 136.2 |
| GFR, mL/min/1.73 m$^2$ | 86.83 | 15.96 | 82.35 | 49.25 | 141.4 |
| Resistive index | 0.671 | 0.041 | 0.67 | 0.6 | 0.74 |
| Parenchymal thickness (PT), mm | 12.24 | 1.98 | 12.1 | 8.1 | 17.2 |

Values are presented as mean±SD or number (%). BMI: body mass index, GFR: Glomerular filtration rate.

## Results

*Demographic and clinical data*

During one month's period, color Doppler ultrasonography for measuring RI and PT and biochemical laboratory testing of urea, creatinine, and GFR were performed in 75 participants from general population, recruited from internal medicine ambulance. Table 1 shows the main demographic and laboratory data as well as RI and PT.

*T-test results*

There were developed two subgroups according kidneys' PT values (subgroup 1 with PT <12.5 mm and subgroup 2 with PT >12.5 mm). The mean value of PT in subgroup 1 is $PT_1$ = 10.78 ± 1.27 mm ($RI_1$ = 0.692 ± 0.038, $age_1$ = 61 years, $N_1$ = 40 participants), and the mean value of PT in subgroup 2 is $PT_2$ = 13.95 ± 1.01 mm ($RI_2$ = 0.648 ± 0.03, $age_2$ = 52.4 years, $N_2$ = 35 participants). The *t*-test for unpaired data between those subgroups with different PT shows a statistically high significance between the mean $RI_1$ and the mean $RI_2$ in two subgroups with different PT [*P* <0.0001, confidence interval (CI) = 0.02808–0.05992].

A graphic presentation of the most important results among two subgroups is shown in Figure 2 which presents the mean, range, median, and 25$^{th}$ and 75$^{th}$ percentiles, 95% CI for the mean, and $RI_1$ and $RI_2$ value for different PT according to different mean RIs by a Box and Whisker diagram. The Box plot diagram shows the mean values of PT in different subgroups and a statistically high significance between kidneys' PT (*P* <0.0001).

*Pearson's correlation*

Negative value of Pearson's product-moment correlation coefficient (*r*) was found as a measure of the strength of linear dependence between two variables (RI as dependent and other independent variables) indicating a significant inverse correlation between the following: RI and GFR ($r$ = −0.352, $P$ = 0.0020), RI and PT ($r$ = −0.284, $P$ = 0.0135), and RI and BMI ($r$ = −0.241, $P$ = 0.037). There is more noticeable pronounced inverse correlation (negative Pearson's "*r*") between RI with relatively reduced PT (PT <12.5 mm, $r$ = −0.275, $P$ = 0.017) than correlation between RI and relatively normal PT (PT >12.5mm, $r$ = −0.351, $P$ = 0.038).

It was established a strong positive correlation between RI and age ($r$ = 0.635, $P$ <0.0001). However, there was computation of a weak inverse correlation ($P$ >0.05) between PT and age ($r$ = −0.226, $P$ = 0.0516).

*Linear regression analysis*

The inverse correlation between two variables (PT and RI) before validated by bivariate correlation is presented by the linear regression equation (equation 1): y = 0.744 + (−0.005932 x). We present another results of linear regression analysis: coefficient of determination

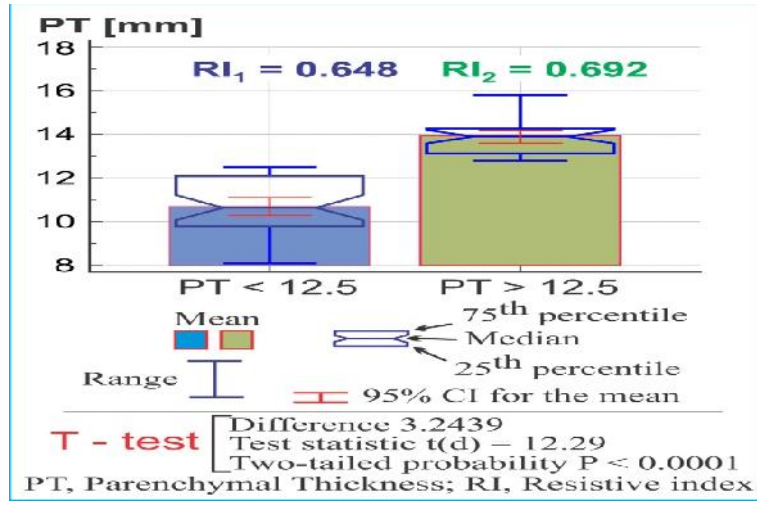


Figure 2. Box plots of the mean, range, median, and 25th and 75th percentiles for parenchymal thickness (PT) according to different mean PT.

$R^2$ = 0.08074, regression parameter $b_0$ = 0.744, regression parameter $b_1$ = −0.005932, residual SD = 0.03991, $P$ = 0.0135, $t$ = −2.5322 (slope), and $P$ <0.0001, $t$ = 25.6096 (intercept). The regression parameter $b_1$ = −0.005932 signified that with each increase of one unit (mm) in thickness of renal parenchyma, the RI score decreased by 0.005932.

Figure 3 shows a scatter plot of linear regression between both kidneys' mean RI and kidneys' mean PT.

The coefficient of determination $R^2$ = 0.1237 as a result of linear regression analysis between RI and GFR ($P$ = 0.0020) showed that 12.37% of the total variability was explained with the linear relation between mean renal RI and mean GFR, or that 12.37% from changing of RI was dependent of GFR. The rest of the total variability between RI and GFR was not explained (100%-12.37% = 87.63%) or more precisely renal RI was dependent on other factors, which were not covered with this regression model. The impact of PT on RI is a step away ($R^2$ = 0.08074) compared with previously explained correlation of the RI and GFR. This $R^2$ showed that 8.074% from

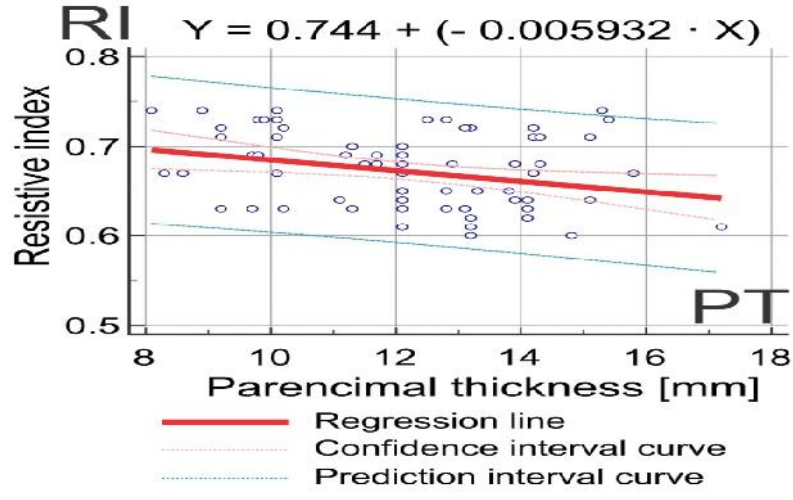


Figure 3. Linear regression analysis and scatter plot of RI and PT.

changing of RI was dependent of PT.

*Multiple regression analysis*

We used multiple regression analysis to show predictable values of independent variables [predictors: age, PT, GFR, BMI, hypertension, (HTN) diabetes and smoking] on the dependent variable renal RI. Because of multicollinearity phenomenon, age was not included in the regression model. Because their statistical $P$ >0.1, BMI, HTN, diabetes, and smoking were not included in model, only GFR and PT with $P$ <0.05 were included. Assessments [standardized coefficient β (βst), standard error of βst, $t$, and $P$ value] on the independent predictor or determinants for increasing of RI in general population after backward multiple regression analysis are shown in Table 2.

The $P$ values followed the order of statistical significance: GFR (0.0012) and PT (0.0078). The coefficient of determination $R^2$ (0.2063) showed that 20.63% of the total variability was explained with the linear regression between RI and GFR, accompanied by PT. A multiple correlation coefficient (0.4542) as the square root of the $R^2$, is a measure of how well a given variable (RI) can be predicted using a linear function of a set of other variables (GFR and PT). Because of their negative value of βst (−0.0009176 and −0.006003), GFR and PT showed an inverse correlation with RI. This means that any reduction of GFR and PT results in an increased RI. We confirm this conclusion with a statistical probability of 99.9988% and 99.9922% for GFR and PT, respectively.

## Discussion

In this prospective longitudinal study we measured the renal PT by B-mode ultrasonography (USG) and renal RI by Doppler USG, and also, blood urea and creatinine in 75 patients from the general population. We aimed to find the associative connections of renal RI index with renal PT and GFR.

Only small-sized studies have evaluated the reference values of renal RI in healthy adults,[9-11] respectively. Most of those studies, as well as this study, have described the constant increasing incidence of renal RI connected with age ($P$ >0.0001) and even suggested a value of RI >0.7 as being pathological without establishing normal values to age. The mean age of this study's sample group was 57.1 years, and the measured values of renal RI were 0.671 ± 0.041. The results of the renal RI

Table 2. Multiple backward regression analysis of determinants of RI.

| **Multiple regression** | | | | |
|---|---|---|---|---|
| Dependent Y | RI | | | |
| Method, backward | Enter variable if $P$<0.05 | | | |
| Sample size | 75 | | | |
| Coefficient of determination $R^2$ | 0.2063 | | | |
| Multiple correlation coefficient | 0.4542 | | | |
| **Regression equation** | | | | |
| **Independent variables** | **βst coefficient** | **Std. error** | ***t*** | ***P*** |
| GFR | −0.0009176 | 0.0002719 | −3.375 | 0.0012 |
| Parenchymal thickness | −0.006003 | 0.002192 | −2.739 | 0.0078 |
| **Analysis of variance** | | | | |
| **Source** | **DF** | **Sum of squares** | **Mean square** | |
| Regression | 2 | 0.02609 | 0.01305 | |
| Residual | 2 | 0.1004 | 0.001394 | |
| F-ratio | 9.3585 | | | |
| Significance level | $P$=0.0002 | | | |

Variables not included in the model: BMI, age, hypertension, diabetes, and smoking.
βst coefficient: Beta standardized coefficient, Std. error: Standard error, GFR: Glomerular filtration rate, DF: Degree of freedom, RI: Resistive index.

range match with the results of other studies,[11-13] beside different ages of estimated population 45–54 years. The mean renal PT in the study's population group was matched with other studies, too. The PT of 13.4 mm for the left and 12.7 mm for the right kidney parenchyma (average: 13.05 mm) was measured in Charles Eze study.[14] It was noted that the renal RI and PT results were variable in different studies regardless of their dependence on age, the functional ability of the kidneys (estimated by GFR), renal disease, and their comorbidity.

Grouping the patients with normal PT (PT >12.5 mm) in the first subgroup and patients with reduced PT (PT <12.5 mm) in the second subgroup, *t*-test for unpaired data between those subgroups with different PT shows a high statistical significance between renal RI according to PT in two different subgroups. This difference in RI according to different PT, estimates that there is probably a relationship between the anatomical variable (PT) obtained with B-mode ultrasonography and the hemodynamic variable (RI) obtained by color Doppler ultrasonography. There was a significant inverse correlation between RI and PT and between RI and GFR. This inverse correlation was slightly more pronounced between RI and reduced PT (PT <12.5 mm) than RI with relatively normal PT. This finding has been confirmed in other studies,[15-17] which highlights the importance of RI changes in patients with reduced PT due to aging or renal disease. Such nonlinear difference in the RI and PT correlation due to the aging and advanced atherosclerosis leads to increasing of RI, because of the renal arteries atherosclerosis. The renal RI correlates with the systemic vascular disease during aging and with chronic kidney disease. Thus, by measuring the renal RI, we obtain combined information about the extent of the local renal impairment and the systemic vascular damage.[18] An increased renal RI not only reflects changes in intrarenal perfusion but was also positively related to systemic hemodynamics and the presence of subclinical atherosclerosis.[1]

There are not enough studies that assess the correlation between GFR and renal RI. The results from this research study match the results from Gaurav et al study.[19] Pearson's correlation coefficient in 310 examined patients demonstrated a significant negative correlation between renal RI and GFR ($r = -0.285$, $P < 0.01$). The results from Parolini et al showed an inverse correlation between renal RI and GFR, too ($r = -0.4$, $P < 0.001$).[20] Their results and the results in this study serve as a pilot assessing the correlation between GFR and RI could provide as an early objective indicator of renal impairment as kidney may appear normally according to PT estimated by B-mode ultrasound.

The inverse correlation between renal RI and PT is presented by equation 1 and scatter plot (Figure 3). The coefficient of determination $R^2$ described that more than 8% from renal RI changes are dependent of PT. The scatter plot would be a good tool for approximate assessment of RI (vertical line, y, ordinate) based on results of PT (horizontal line, x, abscissa). To predict the value of RI, based on a known value of the PP, connect a vertical line from the horizontal axis (x) to the red regression line. At the point where it intersects, draw a parallel line to the vertical axis (y). At the point of intersection, you get the predicted value of the RI, based on the PT value. In this way, with the help of the regression line plot (Figure 3), we can predict the renal RI value without Doppler ultrasound device.

Taking into account the higher coefficient of determination $R^2$ of total variability between RI and GFR, it is understandable that RI estimation by GFR will give more predictable results for parenchymal resistance (i.e., renal RI), because of the data which resulted in more than 12% change of RI as a dependent of GFR. The renal RI as a noninvasive marker of renal histological damage and GFR have been investigated previously.[21,22] In their study, they report that glomerulosclerosis, tubulointerstitial damage, and vascular lesions are directly correlated with an increased RI. Beyond the abovementioned diseases, the renal disease, especially tubulointerstitial damage, correlates inversely with GFR, as well.[23] Lopez-

Giacoman and Madero (2015) concluded that GFR remains an ideal biomarkers to assess the renal function, although it takes more time. GFR equation that combines the results of serum creatinine and cystatin C has proved to be more accurate than equations that use either serum creatinine or cystatin C alone.[24]

The results of multiple regression analysis of determinants of RI showed that PT and GFR inversely are correlated with RI. The patients that were diagnosed with renal parenchyma reduction and GFR, resulted in a noticeable increase of renal RI. The predictive value of independent variable GFR on the dependent variable renal RI was more expressed compared with PT. A multiple correlation coefficient (0.4542) is a measure of how RI can be predicted using a linear function of a set of other variables (GFR and PT). Combining GFT, RI, PT, urine albumin-to-creatinine ratio, and other reasonable biomarkers in urine and plasma, improves risk stratification for kidney disease progression and mortality.[24]

## Limitation of the study

The first limitation of this study was the small number of examined patients. Furthermore, the inclusion of greater number of examined patients will provide better correlation and better predictive values of the PT and GF, according to the RI. The second limitation is the applicability of our conclusions which is limited only to the general population, because there are not enough patients with HTN, interstitial nephropathy, and other kidney diseases, in order to be applicable in patients with advanced renal disease. The third limitation is the impact of the generalized atherosclerosis on the renal artery which generates a relative error during the renal RI measurement. In order to reduce that kind of error, some studies suggest RI measurement on the spleen artery and proper correction on renal RI in accordance to spleen RI,[25] in that way excluding the impact of the generalized atherosclerosis on the atherosclerosis on the renal artery.

## Conclusion

Despite its relatively low specificity and sensitivity in terms of clinical correlation and poorly understood pathogenesis, an increased renal RI has been shown to be a marker of renal damage. Taking all studies into consideration, as a conclusion, we can be highlighted that the renal RI inversely correlates with the PT and GFR determinants, determining them as independent predictors for the increase of RI in the general population.

Doppler ultrasound as a very useful tool provides information about intraparenchymal vascularization through measurement of renal RI and its changes over time. The measurements of RI, PT, and GFR as essential biomarkers acting jointly are an important and powerful tool for assessing renal function. The measurements of RI, PT, and GFR as clinical biomarkers acting jointly are important and powerful tools for assessing renal function. Due to the established correlation with PT and GFR, if Doppler device is not available, the assessment of renal disease would be satisfied only by examining PT and GFR.

**Conflict of interest:** None declared.

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