BMC Nephrology

RESEARCH

Open Access

Association of renal resistive indices with kidney disease progression and mortality

Chloe Kharsa[1], Chadia Beaini[1], Dania Chelala[2] and Mabel Aoun[2*]

Abstract

Background Renal resistive indices (RRI) have been shown to predict the progression of kidney disease. This study aims to evaluate the association of RRI with mortality and dialysis initiation after adjustment to therapeutic and life style interventions.

Methods This is a retrospective study that included all chronic kidney disease patients followed for at least two years in three nephrology clinics between 2006 and 2019 and who had a RRI level in their files. Kaplan Meier and log rank test compared the survival of patients with normal versus high RRI. Cox regression analysis evaluated the association between RRI and death or dialysis initiation after adjustment to treatments and life style modifications.

Results A total of 192 patients were analyzed: 68 had RRI < 0.7 and 124 had RRI ≥ 0.7. Their mean age was 66.5 ± 13.1 years at first visit, 78.1% were males. There was a negative correlation between baseline eGFR and RRI ($p < 0.001$; Spearman correlation coefficient = -0.521). The survival was significantly better in patients with RRI < 0.7 with a Log Rank test < 0.001. The univariate cox regression analysis showed a significant association between RRI and mortality (HR = 1.08; 95%CI: 1.04–1.11; $p < 0.001$) that remained significant after adjustment to cardiovascular risk factors and interventions such as salt reduction, blood pressure control, statins and RAAS inhibitors (HR = 1.04; 95%CI: 1.00–1.08; $p = 0.036$). Cox regression analysis showed a significant association between RRI and dialysis initiation (HR = 1.06; 95%CI 1.01–1.10; $p = 0.011$).

Conclusion Our study revealed that patients with an elevated RRI ≥ 0.7 are at a higher risk of mortality after adjustment to medications and lifestyle modifications. RRI can, according to this study, be considered as an independent prognostic factor in CKD patients.

Keywords Renal resistive index, Chronic Kidney Disease, Hemodialysis, Life style modifications, Mortality

Introduction

Chronic kidney disease (CKD) is defined as an alteration of the kidney function and structure during more than three months [1, 2]. The prevalence of CKD patients is growing significantly affecting at least one in ten adults [3]. This can be explained by improvement in life expectancy, by aging of populations [4] and by the increase of risk factors of kidney diseases [5], such as obesity, hypertension [6] and diabetes [7]. CKD is currently a major global public health issue and it is one of the leading causes of death worldwide [8]. It is still a challenge to determine the prognostic markers of CKD and to evaluate whether these markers are independently associated with outcomes.

Kidney ultrasound (US) is the gold standard imaging to rule out urinary tract obstruction, to assess kidneys' size and corticomedullary differentiation [9]. When kidney US is coupled to a pulsed wave spectral Doppler, vascular velocities in the renal main artery and intra-renal arteries

*Correspondence:
Mabel Aoun
aounmabel@yahoo.fr
[1] Faculty of Medicine, Saint Joseph University of Beirut, Beirut, Lebanon
[2] Department of Nephrology, Faculty of Medicine, Saint Joseph University of Beirut, Beirut, Lebanon

can be evaluated. Doppler US is usually prescribed to diagnose renal artery stenosis. The variation in blood flow velocity with time evaluated by Doppler US makes it possible to calculate the renal resistive index (RRI) [10]. RRI is defined as the maximum blood flow velocity in systole minus the minimum blood flow velocity at the end of diastole over peak systolic velocity. RRI was initially used to evaluate arterial stiffness [11]. The normal value of RRI in an adult varies between 0.47 and 0.7 with a difference that does not exceed 5 to 8% between the two kidneys [12]. RRI directly reflects the vascular impedance, which results from the interaction between pulsatility and vascular compliance [13]. Thus, any condition that decreases vascular compliance and increases pulse pressure induces an increase in RRI, for example advanced age, smoking, hypertension, atherosclerosis and CKD.

RRI has been demonstrated by several researchers as a renal and cardiovascular prognostic marker [14–18]. In hypertensive patients without prior cardiovascular disease, RRI predicted the renal outcome and overall survival [19, 20]. In patients with diabetes, RRI predicted the occurrence of diabetic nephropathy [14, 15]. Elevated RRI seem to reflect the kidney microvasculature and the degree of tubulointerstitial disease [21]. High RRI predicted a resistance to steroid therapy in glomerulonephritis [22]. In transplant patients, the prognostic value of RRI > 0.7 or > 0.8 was also extensively studied [16, 23, 24]. Pulse pressure was found as an independent predictor of high RRI in transplant patients [25] and RRI < 0.8 at 3 months after transplantation was associated with better kidney prognosis [26]. RRI is also useful in the diagnosis of acute kidney injury (AKI) and a cut-off of 0.7 was predictive of postoperative AKI and related-mortality [17, 27]. Despite all these studies highlighting the prognostic role of RRI, physicians are still not using doppler US for this purpose.

Therefore, this study aims to evaluate the association of high RRI with renal outcome and mortality in CKD patients and to assess whether this association persists after adjustment to therapeutic and life style modifications.

Materials and methods

Study design, context and participants

This is a multi-center retrospective study that included CKD patients who consulted at three Lebanese nephrology clinics for the first time between February 2006 and December 2019. Nephrologists following these patients are affiliated to the Faculty of Medicine of the Saint-Joseph University of Beirut.

Eligibility criteria

Patients were included if they were older than 18 years, if they had a renal Doppler US with a RRI level in their file and if they were followed for at least two years. Single (solitary) kidney patients, kidney transplant recipients, patients diagnosed with polycystic kidney disease or renal artery stenosis were excluded.

Data collection

Data collection was conducted between April and September 2022. Baseline data collected from patients' medical files included demographics, date of first visit, number of visits, cardiovascular (CV) risk factors such as hypertension, diabetes, smoking, dyslipidemia, obesity, history of coronary artery disease (CAD), heart failure and/or strokes, laboratory values at the first visit (T1) such as serum creatinine, glomerular filtration rate (GFR) estimated by the 2012 CKD-EPI equation, urine albumin over creatinine ratio (ACR), HbA1c level. RRI levels were collected once from reports of Doppler US at T1 or between the first and second visit. If RRI levels of the two kidneys were different, we recorded the average of both levels.

Follow-up data included the number of visits, date of last visit, laboratory values of serum creatinine, eGFR, ACR and HbA1c at last visit (T2), chronic medications namely statin, proton pump inhibitor (PPI), calcium channel blocker (CCB), renin–angiotensin–aldosterone system (RAAS) inhibitor (Angiotensin-converting enzyme (ACE) inhibitor or angiotensin-receptor blocker), beta-blocker, thiazide diuretic and occurrence of any new cardiovascular event such as coronary event, heart failure, or stroke.

Definitions

CKD is defined in this study based on the KDIGO classification taking into consideration GFR categories and urine albumin to creatinine ratio (ACR) [1]. GFR category is estimated by the 2012 CKD-EPI equation. Stage 1 is an estimated GFR (eGFR) ≥ 90 ml/min/ 1.73 m2 with ACR ≥ 30 mg/g or any other marker of kidney damage, stage 2 is eGFR 60–89 with ACR ≥ 30 mg/g or any other marker of kidney damage, stage 3a is eGFR 45–59, stage 3b is eGFR 30–44, stage 4 is eGFR and stage 5 is eGFR < 15 ml/min/ 1.73 m2.

Life style modifications/ interventions

We collected whether blood pressure was controlled, defined as < 140/90 at the last visit (T2), whether HbA1c was reduced between first and last visit. Other recorded life style modifications were smoking cessation, weight loss and compliance with a low sodium diet. Weight loss

was defined as any weight loss above 2 Kgs between T1 and T2. Patients were considered as compliant to low salt diet based on their statement, and/or their caregiver's confirmation and/or low 24-h urinary salt less than 5 g per day when available. The compliance to medications was assessed by the count of boxes that the patients bring to the clinic in order to renew the unified prescription and to get reimbursed by the national social security fund or the military funds of the country, that constitute 80% of all patients' coverage. For the remaining 20%, we assessed patients' compliance by the renewed prescriptions.

Outcomes

Two outcomes were recorded: death and initiation of dialysis. The time before death and/or dialysis has been determined, as well as the cause of mortality. Another outcome assessed was the three-point major cardiovascular event (3P-MACE) including non-fatal myocardial infarction, non-fatal stroke or cardiovascular death.

Measurements

Radiologists affiliated to the three clinics were well-trained at performing RRI measurement using Doppler US. RRI is defined as the maximum blood flow velocity in systole minus the minimum blood flow velocity at the end of diastole over peak systolic velocity.

The laboratory biological parameters including creatinine level, ACR and HbA1c were measured using standard techniques in the three hospitals' labs.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences, Version 24.0 (SPSS Inc.-IBM corp., Armonk, NY, USA). Continuous data were reported as mean and standard deviation (SD) if normally distributed and as median and interquartile (IQR) if skewed. Categorical data were reported as numbers and percentages. Missing data was estimated at 7.8% for compliance to salt reduction, 6% for smoking cessation, 11.5% for weight loss and 49.5% for ACR (T2). ACR at T2 was removed from the analysis. Little's MCAR test showed that compliance to salt reduction, smoking cessation and weight loss were missing completely at random. We performed a multiple imputation regression model to replace the missing values. The imputed data was used to analyze the multivariable cox regression model and the results were similar to the original model. Mann Whitney test, independent t-test, Chi Square test were used to compare two groups of RRI levels. Spearman rho correlation evaluated the correlation between two continuous variables. The receiver operating curve (ROC) analysis was used to assess the predictive value of RRI for dialysis and death. Kaplan Meier survival analysis and log rank test evaluated the difference in survival between patients with normal and high RRIs. Cox regression analysis assessed the factors associated with death and the association between RRI and dialysis. A Cox proportional hazards regression analysis was performed to assess factors associated with death, dialysis and 3P-MACE; the first model included all cardiovascular risk factors, the second, third and fourth models added to Model 1 renal factors, therapeutic and preventive interventions. P-value < 0.05 was considered as statistically significant.

Results

Flowchart diagram

Among the 1600 medical files reviewed in three different clinics, 289 patients responded to the inclusion criteria (the major reason for non-inclusion was the absence of RRI level in the medical file). Were excluded: 23 kidney transplants, 36 solitary kidneys and 38 polycystic kidney disease patients. Finally, a total of 192 CKD patients responded to inclusion and exclusion criteria (Fig. 1).

General characteristics

Out of the 192 patients analyzed, 124 had a RRI ≥ 0.7. Table 1 summarizes their baseline characteristics. Their mean age was 66.5 ± 13.1 years at first visit, 78.1% were males, 95.8% of them were hypertensive. Their mean follow-up was 73.4 ± 41.5 months.

The Spearman correlation coefficient showed a negative correlation between baseline eGFR and RRI (coefficient = -0.521, $P < 0.001$) (Fig. 2).

Medications and life style modifications

Percentages of patients treated with calcium channel blockers, proton pump inhibitors and beta blockers were higher in the group with a RRI ≥ 0.7 compared to the group with normal RRI.

Over the course of consultations, cardiovascular risk factors were less controlled in patients with a RRI ≥ 0.7. Moreover, only 48% managed their blood pressure and 36% followed a low-sodium diet in contrast to patients with a normal RRI, of whom 71% controlled their BP and 54% followed a low-salt diet (Table 2).

Complications during follow-up and outcomes

Patients with high RRI ≥ 0.7 had higher rates of doubling of serum creatinine, of initiation dialysis and of death (Table 3). The survival curve obtained during the Kaplan Meier analysis of the two groups shows a better life expectancy in patients with a normal renal resistive index with Log Rank < 0.001 (Fig. 3).

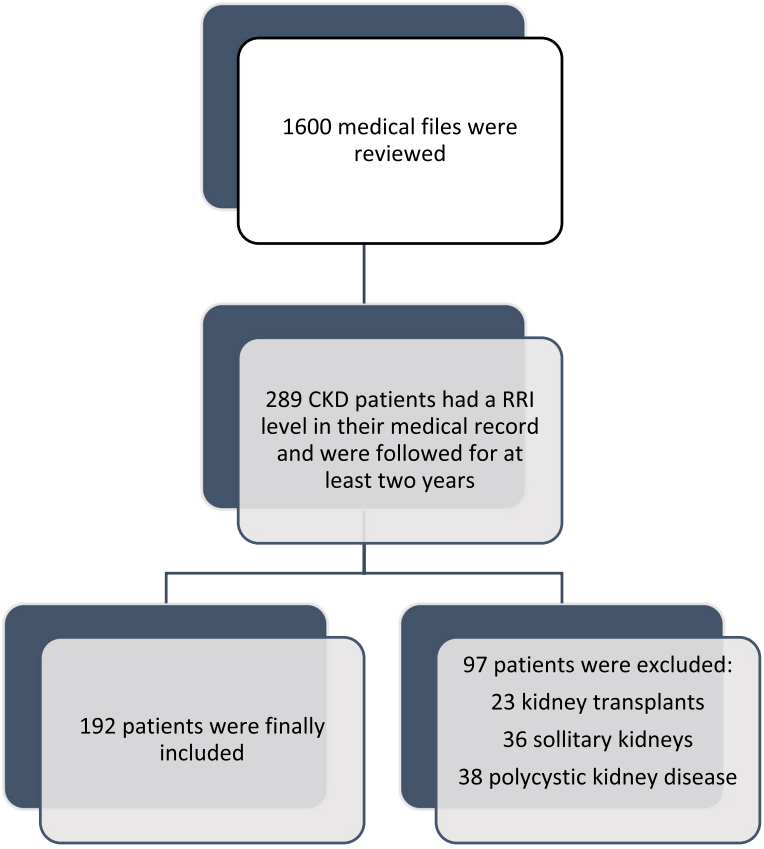

Fig. 1 Flow diagram of patients' inclusion

The area under ROC curve for RRI predicting death is 0.667 (Fig. 4), and the area under ROC curve for RRI predicting dialysis is 0.654 (Fig. 5).

Factors associated with dialysis occurrence

Cox regression analysis showed that baseline elevated RRI, lower eGFR, high levels of albuminuria were risk factors associated with dialysis occurrence (Table 4). RAAS inhibitors, compliance to salt reduction and control of BP to less than 140/90 were all protective factors (Table 4). The number of visits over follow-up duration was significantly associated with dialysis (Table 4).

After adjusting to cardiovascular risk factors, RRI remained an independent risk factor associated with dialysis (Table 5 and Table S1). RRI was no more associated with dialysis after adjustment to eGFR, ACR, treatments and lifestyle modifications (Table 5 and Table S1).

Factors associated with mortality

Cox regression analysis showed a significant association between RRI and death (HR: 1.08; CI: 1.04–1.11; $P<0.001$) (Table 6). Age, CAD, heart failure, low eGFR, beta-blockers were also factors associated with excess death whereas taking a RAAS inhibitor was protective (Table 6).

After adjusting to cardiovascular risk factors, renal factors, treatments and lifestyle modifications, RRI remained an independent risk factor associated with death (Table 7 and Table S2).

Factors associated with 3P-MACE

Logistic regression analysis showed a significant association between RRI and 3P-MACE (HR: 1.05; CI:1.02–1.09; $P=0.001$), that remained significant after adjustment to CV risk factors (HR = 1.04; CI:1.01–1.07; $P=0.039$). This association was not statistically significant after adding eGFR and albuminuria to demographics and CV risk factors (HR = 1.03; CI:0.99–1.06; $P=0.130$) and after further adding of treatment and lifestyle modifications (HR = 1.04; CI:0.99–1.08; $P=0.070$).

Discussion

This study confirms RRI as an independent factor associated with death in patients with CKD. According to our results, an increase of 0.01 in RRI increases the death by 7% after a mean follow-up of 73 months. This association

Table 1 General characteristics of patients divided into normal and high RRI

Variable	Total *N* = 192	Patients with RRI < 0.7 *N* = 68	Patients with RRI ≥ 0.7 *N* = 124	*P*
Demographics				
Age at first consultation, y Mean ± SD	66.5 ± 13.1	58.7 ± 12.7	70.7 ± 11.2	< 0.001
Sex (M/F), n(%)	150/42 (78.1/21.9)	54/11 (79.4/20.6)	96/28 (77.4/22.6)	0.75
Smoking, n(%)	83 (43.2)	32 (47.1)	51(41.1)	0.33
Obesity, n(%)	65 (33.9)	27 (39.7)	38 (30.6)	0.17
Cardiovascular risk factors				
Hypertension, n(%)	184 (95.8)	64 (94.1)	120 (96.8)	0.38
Diabetes, n(%)	93 (48.4)	23 (33.8)	70 (56.5)	0.003
Dyslipidemia, n(%)	152 (79.2)	48 (70.6)	104 (83.9)	0.03
History of CAD, n(%)	56 (29.2)	13 (19.2)	43 (34.6)	0.02
History of stroke, n(%)	14 (7.3)	3 (4.4)	11 (8.9)	0.26
History of heart failure, n(%)	16 (8.3)	3 (4.4)	13 (10.5)	0.15
Cause of CKD, n(%)				
• Diabetic nephropathy	93 (48.4)	23 (33.8)	70 (56.5)	0.01
• Cardiorenal syndrome	3 (1.6)	0	3 (2.4)	
• Glomerular disease	2 (1)	1 (1.5)	1 (0.8)	
• Undetermined or tubulointerstitial nephritis or nephrosclerosis	94 (49)	44 (64.7)	50 (40.3)	
Laboratory parameters T1				
Serum creatinine T1, mg/dL Median (IQR)	1.6 (1.2–2.2)	1.3 (0.9–1.6)	1.8 (1.4–2.6)	< 0.001
eGFR, mL/min/1.73m2 T1	40 (28–57.8)	59 (40.8–81.8)	35 (22.3–45)	< 0.001
Stage of CKD T1, n(%)				
• Stage 1	16 (8.3)	13 (19.1)	3 (2.4)	< 0.001
• Stage 2	31 (16.1)	21 (30.9)	10 (8.1)	
• Stage 3a	33 (17.2)	14 (20.6)	19 (15.3)	
• Stage 3b	58 (30.2)	14 (20.6)	44 (35.5)	
• Stage 4	46 (24)	6 (8.8)	40 (32.3)	
• Stage 5	8 (4.2)	0	8 (6.5)	
ACR T1, mg/g Median (IQR)	194 (29–1000)	66 (12.5–263)	500 (47.5–1650)	< 0.001
HbA1c T1 (if diabetes) Median (IQR)	6.9 (6–7.9)	7.3 (6.4–9.6)	7.1 (6.5–8.2)	0.63
RRI, T1 Median (IQR)	0.73 (0.65–0.80)	0.6 (0.6-0.65)	0.8 (0.73-0.85)	< 0.001

is sustained after adjustment to cardiovascular risk factors, kidney function, ACR, therapeutic and lifestyle interventions. Our results concur with Toledo et al. who analyzed 1962 patients with CKD stages 3 and 4 and found that RRI > 0.7 was associated with higher mortality [18]. Similarly, Romano et al. followed 131 patients with a mean age of 76 years, for a median of 7.5 years and found that patients with RRI ≥ 0.80 had a faster kidney function loss and higher mortality [28], and similar to our results, their AUROCs of RRI for predicting mortality and progression of renal disease were 0.67 and 0.66 respectively [28]. Leodori et al. followed also 122 patients with systemic sclerosis and different levels of eGFR and demonstrated that RRI is an independent predictor of mortality [29].

Another important finding in our study is the strong correlation between RRI and eGFR at baseline. This has been previously described by several researchers. Kosaki et al. recently demonstrated that patients with CKD have an increased intrarenal pulsatility and an elevated RRI [30]. Sistani et al. showed significant association between RRI and GFR and albuminuria among 100 patients with diabetic nephropathy [31]. Bigé et al. evaluated RRI levels in 58 patients two days prior to kidney biopsy and found a

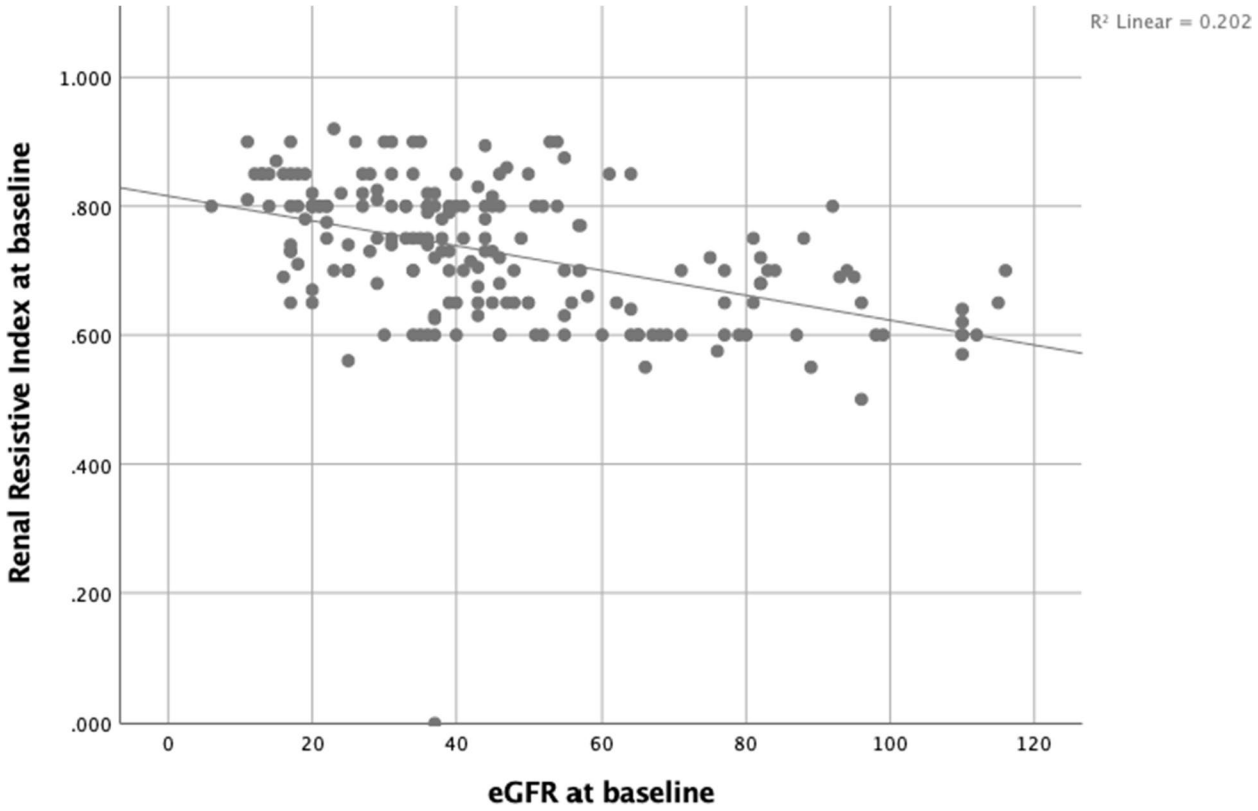

Fig. 2 Correlation between RRI and eGFR at baseline

Table 2 Follow-up: treatment and lifestyle modifications

Variable	Total *N* = 192	Patients with RRI < 0.7 *N* = 68	Patients with RRI ≥ 0.7 *N* = 124	*P*
Treatment				
Statin, n(%)	124 (64.6)	44 (64.7)	80 (64.5)	0.979
ACE inhibitor, n(%)	26 (13.5)	12 (17.6)	14 (11.3)	0.203
Angiotensin Receptor Blocker, n(%)	105 (54.7)	39 (57.4)	66 (53.2)	0.509
Thiazide, n(%)	30 (15.6)	8 (11.8)	22 (17.7)	0.293
CCB, n(%)	121 (63)	37 (54.4)	84 (67.7)	0.087
PPI, n(%)	48 (25)	11 (16.2)	37 (29.8)	0.041
Antiaggregant agent, n(%)	86 (44.8)	26 (38.2)	60 (48.4)	0.204
Beta-blocker, n(%)	113 (58.9)	29 (42.6)	84 (67.7)	0.001
Number of antihypertensive molecules, Mean ± SD	2.07 ± 0.96	1.87 ± 0.89	2.18 ± 0.99	0.027
Follow-up, interventions/lifestyle modifications				
Duration of follow-up, months Mean ± SD	73.4 ± 41.5	85.8 ± 46.6	66.6 ± 36.8	0.002
Number of consultations during follow-up (before dialysis), months Median (IQR)	5 (3–10.8)	4 (2–6.8)	6 (3–12)	0.002
Control of hypertension < 140/90, n(%)	108 (56.3)	48 (70.6)	60 (48.4)	0.006
HbA1c reduction in patients with diabetes, n(%)	46 out of 93 (49.5)	14 out of 23 (61)	33 out of 70 (47.1)	0.460
Weight loss, n(%)	60 (31.3)	23 (33.8)	37 (29.8)	0.490
Smoking cessation among smokers, n(%)	13 out of 83 (15.7)	8 out of 32 (25)	6 out of 51 (11.8)	0.100
Compliance to salt reduction, n(%)	82 (42.7)	37 (54.4)	45 (36.3)	0.009

Table 3 Follow-up: complications, renal outcomes and death

Variable	Total *N* = 192	Patients with RRI < 0.7 *N* = 68	Patients with RRI ≥ 0.7 *N* = 124	*P*
Complications during follow-up				
Coronary event, n(%)	31 (16.1)	13 (19.1)	18 (14.5)	0.313
Stroke, n(%)	8 (4.2)	3 (4.4)	5 (4)	0.851
Heart failure, n(%)	12 (6.3)	4 (5.9)	8 (6.5)	0.915
Outcomes				
Serum creatinine, mg/dL T2 Median (IQR)	1.9 (1.1–4.5)	1.2 (0.9–1.9)	2.5 (1.5–5.9)	< 0.001
eGFR, mL/min/1.73m2 T2 Median (IQR)	33.5 (10.3–60.8)	61 (31–87)	22.5 (8–42.8)	< 0.001
Doubling of serum creatinine, n(%)	42 (21.9)	6 (8.8)	36 (29)	0.001
Dialysis, n(%)	40 (20.8)	8 (11.8)	32 (25.8)	0.022
Duration of follow-up until dialysis, months Mean ± SD	38.2 ± 25.4	63.5 ± 28.1	31.8 (20.6)	< 0.001
Death, n(%)	54 (28.1)	12 (17.6)	42 (33.9)	0.017
Cause of death, n(%)				
• Cardiac cause	26 (13.5)	6 (8.8)	20 (16.1)	0.02
• Stroke	1 (0.5)	0	1 (0.8)	
• Cancer	13 (6.8)	5 (7.4)	8 (6.5)	
• Infection	3 (1.5)	0	3 (2.4)	
• COVID	8 (4.2)	0	8 (6.5)	
• Bleeding	1 (0.5)	0	1 (0.8)	
• Cirrhosis	1 (0.5)	1 (1.5)	0	
• Trauma	1 (0.5)	0	1 (0.8)	

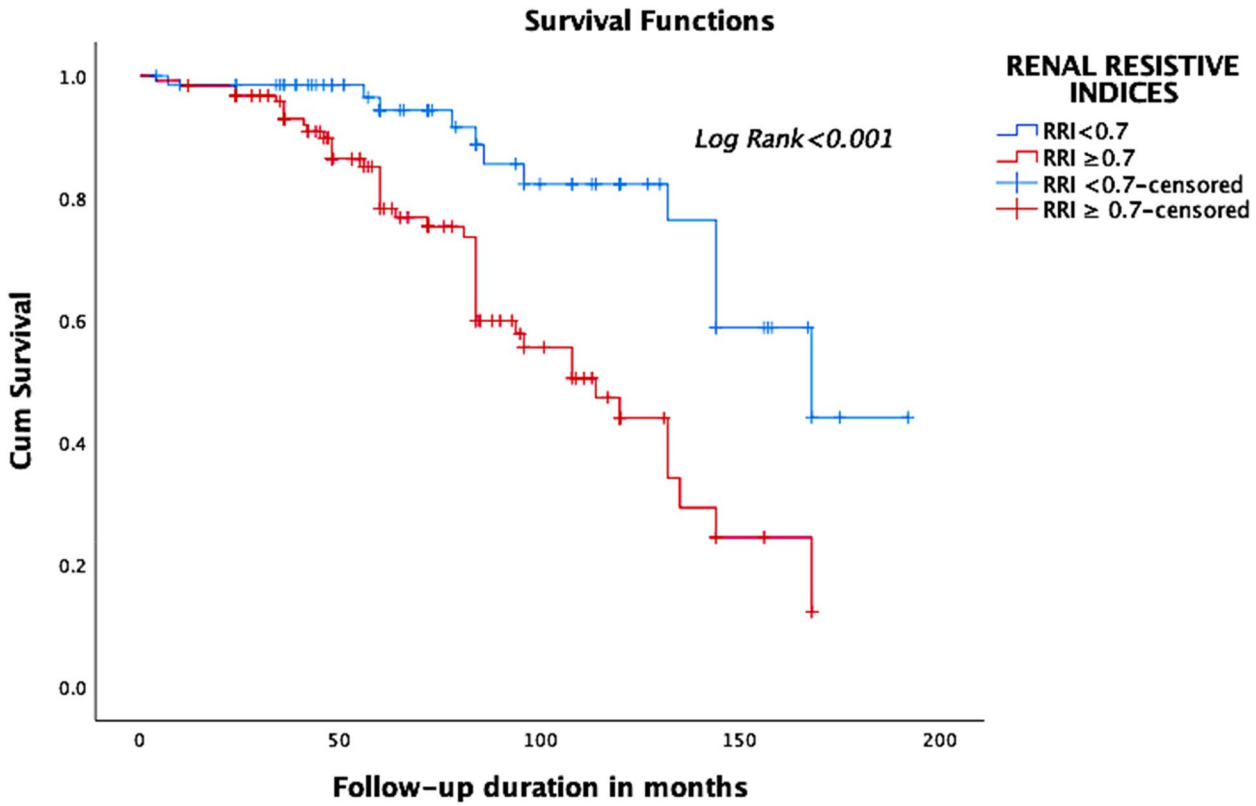

Fig. 3 Survival curve of two groups of RRIs

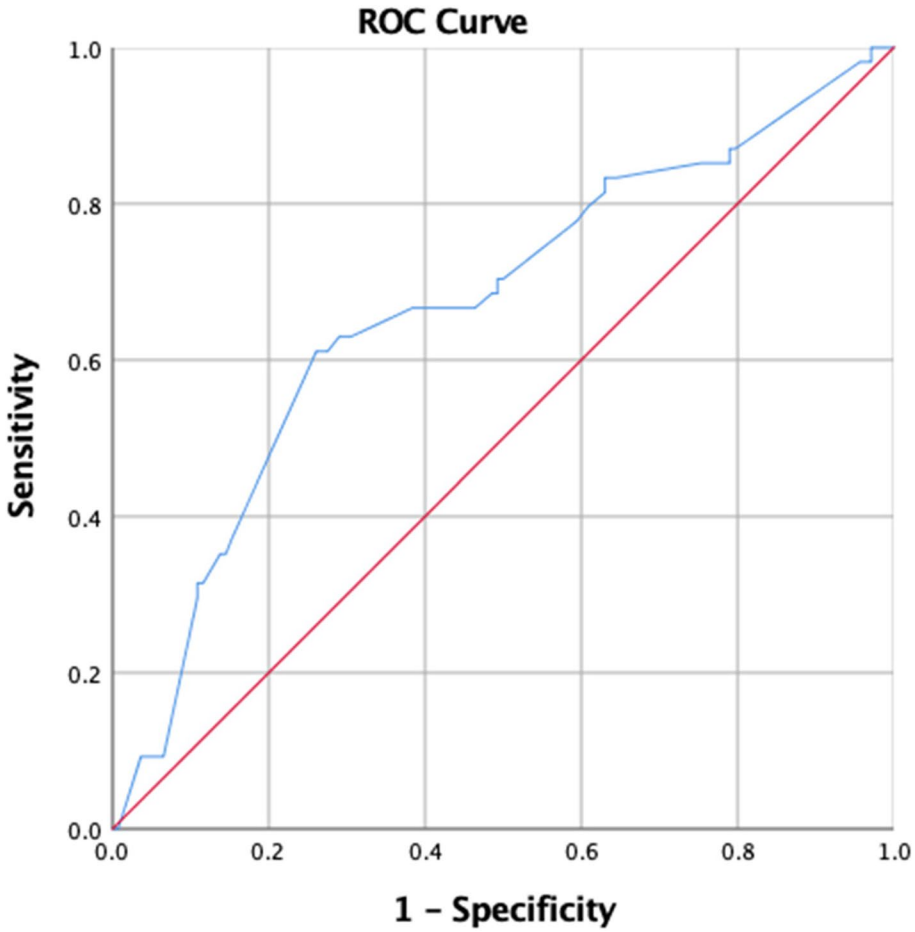

Fig. 4 Area under the ROC curve of RRI predicting death

strong correlation between RRI and interstitial fibrosis as well as accelerated kidney function decline independent of baseline eGFR [32]. This strong association between eGFR and RRI suggest that the outcomes driven by RRI depend on the kidney function. This might be true for dialysis in our study but not for mortality. In fact, Toledo et al. showed also that the association of RRI with mortality remained significant after adjustment to the kidney function [18]. Regarding the dialysis outcome, our study revealed a significant association between RRI and the progression to dialysis. However, in contrast to mortality, the association of RRI and dialysis was no longer statistically significant after adjusting to different comorbidities. On the contrary, Parolini et al. followed 86 patients with CKD for 2–11 years and found out that RRI ≥ 0.7 was an independent risk factor for the progression to renal failure, independent of initial eGFR [33]. Barone et al. recently showed that a high RRI was a predictive factor for deterioration of renal function after coronary angiography [34].

One of the main objectives of this study was to evaluate the RRI value in predicting dialysis or mortality, after adjusting to nephroprotective treatment and lifestyle modifications. This was an indirect way to assess whether RRI prognostic value could be modified after implementing appropriate therapeutic and preventive interventions. In fact, very few studies assessed the direct impact of treatment on RRI. Yamaguchi et al. studied 100 CKD patients treated with RAAS inhibitors and who had two measures of RRI [35]. They found that RAAS inhibitors could lower RRI levels [35]. Leoncini et al. compared a small sample of patients treated with lisinopril versus nifedipine; they found more significant reduction in RRI under lisinopril [36]. Our analysis showed that RAAS inhibitors had a protective impact both on death and dialysis, however RRI remained an independent prognostic factor for mortality after adjusting to RAAS inhibitors. The retrospective design of our study does not allow us to draw strong conclusions but it is a call for future interventional studies to assess the long-term effect of RAAS

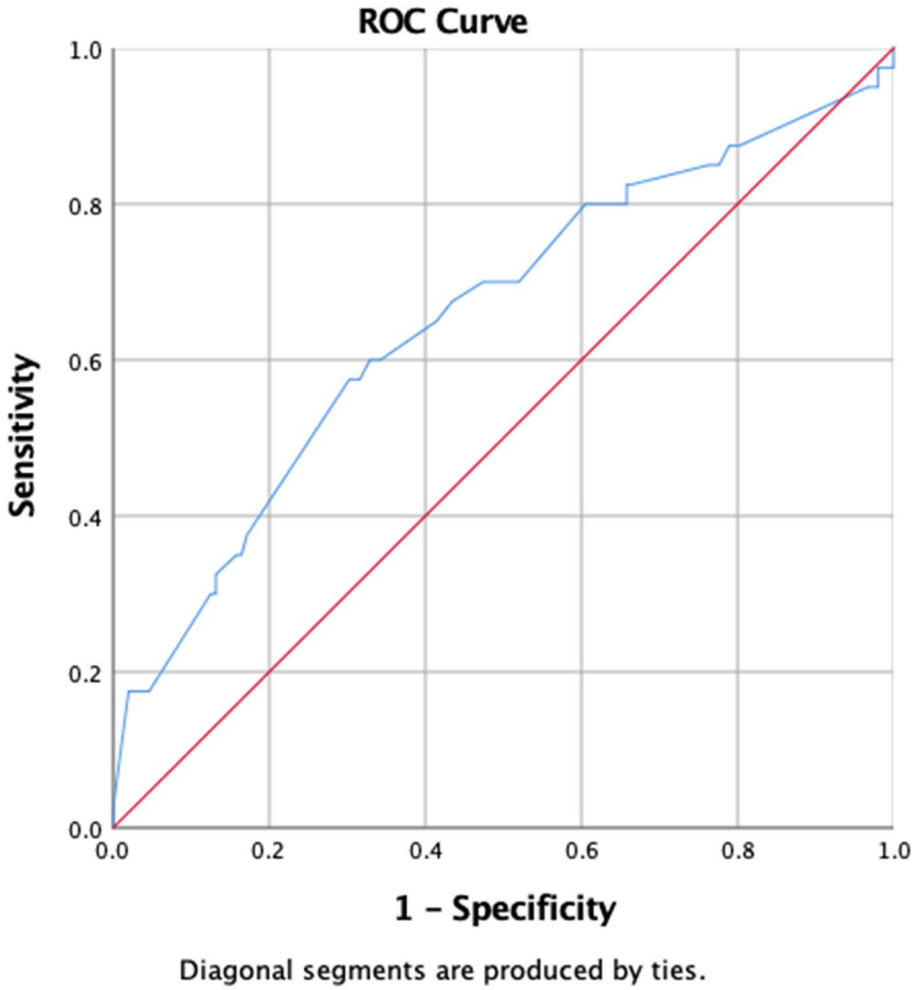

Fig. 5 Area under the ROC curve of RRI predicting dialysis

inhibitors on RRI. Many studies have already proven the cardiovascular protection of RAAS inhibitors in chronic kidney disease patients but they have not stratified their patients into low and high RRI [37].

The other factor that emerged as protective against dialysis in the subgroup of patients with diabetes was the compliance to salt reduction. In fact, many studies have shown the beneficial effect of dietary sodium restriction on kidney function and the positive synergistic effect of RAAS blockade combined to salt reduction [38]. Unfortunately, the definition of compliance to salt reduction in our study was not always based on the 24-h urine sodium but also on patients and caregivers' statements which could be subject to bias. This is another call for interventional trials to assess RRI levels before and after compliance to salt reduction, specifically in patients with diabetes.

Limitations and strengths

To the best of our knowledge, this is the first study analyzing the prognostic character of RRI in CKD patients after adjustment to therapeutic and preventive interventions. Although some might argue that RRI can be operator-dependent, all RRI measurements were performed by well-trained radiologists who are referees in kidney Doppler US in our country. Despite this fact, we admit that some slight variations might occur due to different operators. On the other hand, some limitations should be noted. The major limitation remains in the retrospective nature of our study and the absence of Doppler US after implementation of treatment and life style modifications. A second limitation is the possible bias in patient selection; it is not clear why some patients underwent renal Doppler US while others did not. This limitation makes our findings generalizable only for patients who

Table 4 Cox regression analysis of factors associated with dialysis (univariate analysis)

	Univariate analysis		
	HR	**95% Confidence Interval**	***P***
RRI	1.05	1.02–1.09	0.003
Age	1.01	0.98–1.03	0.762
Sex (*Ref: Male***)**	0.60	0.25–1.44	0.255
Diabetes	1.95	1.03–3.67	0.040
Dyslipidemia	1.65	0.69–3.93	0.259
Obesity	0.95	0.49–1.85	0.880
CAD	1.65	0.87–3.13	0.127
Heart failure	1.76	0.69–4.49	0.238
Stroke	0.83	0.20–3.45	0.797
eGFR, mL/min	0.90	0.88–0.93	< 0.001
ACR, g/g	1.51	1.36–1.69	< 0.001
RAAS inhibitors	0.49	0.27–0.93	0.028
Statins	0.76	0.41–1.44	0.404
Beta-blockers	1.94	0.98–3.83	0.056
Antiaggregants	1.56	0.83–2.91	0.167
PPIs	1.23	0.63–2.42	0.548
BP control < 140/90	0.44	0.23–0.82	0.010
Compliance to salt reduction	0.22	0.09–0.50	< 0.001
HbA1c reduction in patients with diabetes	0.73	0.32–1.65	0.442
Smoking cessation in smokers	0.56	0.13–2.46	0.443
Number of visits over follow-up duration	7.89	4.63, 13.43	< 0.001

Hypertension was not assessed because the vast majority had hypertension; RRI was multiplied by 100

Table 5 Cox proportional hazards models associated with dialysis

	Multivariable analysis		
	HR	**95% Confidence Interval**	***P***
MODEL 1 (CV risk factors)			
RRI	1.06	1.01–1.10	0.012
MODEL 2 (CV risk factors, renal factors, treatment and lifestyle modifications)			
RRI	0.99	0.96–1.04	0.830
MODEL 3 (Subgroup of patients with diabetes)			
RRI	1.09	0.99–1.21	0.081

Model 1 adjusted to: Age, sex, dyslipidemia, obesity, CAD, diabetes, heart failure, history of stroke, number of antihypertensives

Model 2 included Model 1 + eGFR, ACR, RAASi, statins, beta-blockers, antiaggregants, compliance to salt reduction, control of BP < 140/90

Model 3 included Model 2 + HbA1c reduction

Table 6 Cox regression analysis of factors associated with death (univariate analysis)

	Univariate analysis		
	HR	**95% Confidence Interval**	***P***
RRI	1.08	1.04–1.11	< 0.001
Age	1.04	1.02–1.07	0.001
Sex (*Ref: Male***)**	1.60	0.89–2.87	0.118
Diabetes	1.40	0.82–2.39	0.224
Dyslipidemia	0.77	0.41–1.44	0.410
Obesity	0.75	0.42–1.35	0.334
CAD	2.19	1.26–3.80	0.008
Heart failure	2.28	1.11–4.68	0.025
Stroke	0.54	0.07–3.96	0.546
eGFR, mL/min	0.97	0.96–0.98	< 0.001
ACR, g/g	1.13	0.99–1.28	0.058
RAAS inhibitors	0.41	0.24–0.69	0.001
Statins	0.63	0.37–1.08	0.093
Beta-blockers	1.93	1.08–3.46	0.027
Antiaggregants	1.46	0.85–2.51	0.176
PPIs	0.69	0.36–1.34	0.273
Number of antihypertensives	0.86	0.64–1.16	0.325
BP control < 140/90	0.90	0.53–1.54	0.703
HbA1c reduction in patients with diabetes	0.99	0.49–2.01	0.997
Salt reduction	0.68	0.38–1.23	0.207
Smoking cessation in smokers	0.34	0.08–1.43	0.141
Number of consultations	0.99	0.96, 1.02	0.394

Table 7 Cox proportional hazards models associated with death

	Multivariable analysis		
	HR	**95% Confidence Interval**	***P***
MODEL 1 (CV risk factors)			
RRI	1.07	1.03–1.11	< 0.001
MODEL 2 (CV Risk factors and renal factors)			
RRI	1.04	0.99–1.07	0.030
MODEL 3 (CV risk factors, renal factors, treatment and lifestyle modifications)			
RRI	1.05	1.00–1.08	0.020
MODEL 4 (Subgroup of patients with diabetes)			
RRI	1.07	0.98–1.18	0.119

Model 1 adjusted to: Age, sex, dyslipidemia, obesity, CAD, diabetes, heart failure, history of stroke, number of antihypertensives

Model 2 included Model 1 + eGFR, ACR,

Model 3 included Model 2 + RAASi, statins, beta-blockers, antiaggregants, compliance to salt reduction, control of BP < 140/90

Model 3 included Model 3 + HbA1c reduction

underwent RRI measurement. The reasons behind RRI measurement in included patients are most of all the fact that these patients got their renal ultrasound by one of the radiologists who measure systematically RRI, the second less common cause is the decline in renal function following RAASi. The third limitation is related to the definition of compliance to salt reduction that was not homogenous in all cases.

Conclusion

The renal resistive index is an important diagnostic and prognostic element to consider in the renal and cardiovascular evaluation and management of chronic kidney disease. It appears as a very sensitive prognostic marker, predicting progression to an advanced stage of renal failure or death. Despite lifestyle changes and compliance to therapeutic interventions, RRI seems to be an independent prognostic marker of mortality and a diagnostic tool reflecting the severity of renal disease.

Abbreviations

RRI	Renal resistive index or indices
CKD	Chronic kidney disease
GFR	Glomerular filtration rate
CV	Cardiovascular
CAD	Coronary artery disease
ACR	Albumin to creatinine ratio
PPI	Proton pump inhibitor
CCB	Calcium channel blocker
RAAS	Renin–angiotensin–aldosterone system
ACE	Angiotensin-converting enzyme

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12882-023-03398-6.

Additional file 1: Table S1. Cox regression analysis of factors associated with dialysis (multivariable analysis). **Table S2.** Cox regression analysis of factors associated with death (multivariable analysis).

Authors' contributions

C.K. and M.A. contributed to the conceptualization and methodology. C.K., C.B., D.C. and M.A. contributed to the data collection. M.A. contributed to the statistical analysis. C.K. wrote the first draft. M.A. and D.C. made the first revision of the manuscript. All authors reviewed the manuscript.

Funding

No funding.

Availability of data and materials

The dataset supporting the conclusions of this article is included within the article (and its additional file).

Declarations

Ethics approval and consent to participate

This study has been evaluated and approved by the ethics committee of the Faculty of Medicine- Saint Joseph University (Tfem/2022/44). It has been conducted in accordance with the ethical principles set out in the Declaration of Helsinki of the World Medical Association of 1975. The requirement for informed consent was waived by the ethics committee due to the retrospective nature of the study.

Competing interests

The authors declare no competing interests.

Received: 27 August 2023 Accepted: 13 November 2023
Published online: 28 November 2023

References

1. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2013;3:1–150.
2. Levey AS, Coresh J. Chronic kidney disease. The Lancet. 2012;379(9811):165–80. https://doi.org/10.1016/S0140-6736(11)60178-5.
3. Kovesdy CP. Epidemiology of chronic kidney disease: an update 2022. Kidney Int Suppl (2011). 2022;12(1):7–11. https://doi.org/10.1016/j.kisu.2021.11.003
4. Hoerger TJ, Simpson SA, Yarnoff BO, et al. The Future Burden of CKD in the United States: A Simulation Model for the CDC CKD Initiative. Am J Kidney Dis. 2015;65(3):403–11. https://doi.org/10.1053/j.ajkd.2014.09.023.
5. GBD Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2020;395(10225):709–33. https://doi.org/10.1016/S0140-6736(20)30045-3.
6. Kjeldsen SE. Hypertension and cardiovascular risk: General aspects. Pharmacol Res. 2018;129:95–9. https://doi.org/10.1016/j.phrs.2017.11.003.
7. de Boer IH, Caramori ML, Chan JCN, et al. Executive summary of the 2020 KDIGO Diabetes Management in CKD Guideline: evidence-based advances in monitoring and treatment. Kidney Int. 2020;98(4):839–48. https://doi.org/10.1016/j.kint.2020.06.024.
8. Rhee CM, Kovesdy CP. Epidemiology: Spotlight on CKD deaths—increasing mortality worldwide. Nat Rev Nephrol. 2015;11(4):199–200. https://doi.org/10.1038/nrneph.2015.25.
9. Meola M, Samoni S, Petrucci I. Imaging in Chronic Kidney Disease. Contrib Nephrol. 2016;188:69–80. https://doi.org/10.1159/000445469.
10. Petrucci I, Clementi A, Sessa C, Torrisi I, Meola M. Ultrasound and color Doppler applications in chronic kidney disease. J Nephrol. 2018;31(6):863–79. https://doi.org/10.1007/s40620-018-0531-1.
11. Okura T, Watanabe S, Miyoshi K ichi, Fukuoka T, Higaki J. Intrarenal and carotid hemodynamics in patients with essential hypertension*: American Journal of Hypertension. 2004;17(3):240–244. https://doi.org/10.1016/j.amjhyper.2003.10.005
12. Darmon M, Schnell D, Zeni F. Doppler-Based Renal Resistive Index: A Comprehensive Review. In: Vincent JL, ed. Yearbook of Intensive Care and Emergency Medicine 2010. Yearbook of Intensive Care and Emergency Medicine. Springer; 2010:331–338. https://doi.org/10.1007/978-3-642-10286-8_31
13. Bude RO, Rubin JM. Relationship between the resistive index and vascular compliance and resistance. Radiology. 1999;211(2):411–7. https://doi.org/10.1148/radiology.211.2.r99ma48411.
14. Nosadini R, Velussi M, Brocco E, et al. Increased renal arterial resistance predicts the course of renal function in type 2 diabetes with microalbuminuria. Diabetes. 2006;55(1):234–9.
15. Bruno RM, Daghini E, Landini L, et al. Dynamic evaluation of renal resistive index in normoalbuminuric patients with newly diagnosed hypertension or type 2 diabetes. Diabetologia. 2011;54(9):2430–9. https://doi.org/10.1007/s00125-011-2148-y.
16. Radermacher J, Mengel M, Ellis S, et al. The renal arterial resistance index and renal allograft survival. N Engl J Med. 2003;349(2):115–24. https://doi.org/10.1056/NEJMoa022602.
17. Boddi M, Bonizzoli M, Chiostri M, et al. Renal Resistive Index and mortality in critical patients with acute kidney injury. Eur J Clin Invest. 2016;46(3):242–51. https://doi.org/10.1111/eci.12590.
18. Toledo C, Thomas G, Schold JD, et al. Renal resistive index and mortality in chronic kidney disease. Hypertension. 2015;66(2):382–8. https://doi.org/10.1161/HYPERTENSIONAHA.115.05536.

19. Doi Y, Iwashima Y, Yoshihara F, Kamide K, Hayashi S, Kubota Y, Nakamura S, Horio T, Kawano Y. Renal resistive index and cardiovascular and renal outcomes in essential hypertension. Hypertension. 2012 Sep;60(3):770–7. https://doi.org/10.1161/HYPERTENSIONAHA.112.196717. Epub 2012 Jul 23. PMID: 22824987.
20. Radermacher J, Ellis S, Haller H. Renal resistance index and progression of renal disease. Hypertension. 2002;39(2 Pt 2):699–703. https://doi.org/10.1161/hy0202.103782.
21. Agarwal R. Why does renal resistive index predict mortality in chronic kidney disease? Hypertension. 2015;66(2):267–9. https://doi.org/10.1161/HYPERTENSIONAHA.115.05690. (Epub 2015 Jun 15 PMID: 26077570).
22. Hanamura K, Tojo A, Kinugasa S, Asaba K, Fujita T. The resistive index is a marker of renal function, pathology, prognosis, and responsiveness to steroid therapy in chronic kidney disease patients. Int J Nephrol. 2012;2012:139565. https://doi.org/10.1155/2012/139565. Epub 2012 Dec 16. PMID: 23304501; PMCID: PMC3533455.
23. Akgul A, Ibis A, Sezer S, et al. Early assessment of renal resistance index and long-term renal function in renal transplant recipients. Ren Fail. 2009;31(1):18–24. https://doi.org/10.1080/08860220802546347. (PMID: 19142805).
24. Naesens M, Heylen L, Lerut E, et al. Intrarenal resistive index after renal transplantation. N Engl J Med. 2013;369(19):1797–806. https://doi.org/10.1056/NEJMoa1301064.
25. Akgul A, Sasak G, Basaran C, Colak T, Ozdemir FN, Haberal M. Relationship of renal resistive index and cardiovascular disease in renal transplant recipients. Transplant Proc. 2009;41(7):2835–7. https://doi.org/10.1016/j.transproceed.2009.07.023. (PMID: 19765450).
26. Smyrli M, Tsouka G, Oikonomaki T, Apostolou T, Vougas V. Resistive Renal Index of the Recipient and its Correlation With the Outcome of Kidney Transplantation at the End of the First Year: Preliminary Results. Transplant Proc. 2021;53(9):2760–4. https://doi.org/10.1016/j.transproceed.2021.08.033. (Epub 2021 Sep 24 PMID: 34565580).
27. Marty P, Szatjnic S, Ferre F, et al. Doppler renal resistive index for early detection of acute kidney injury after major orthopaedic surgery: a prospective observational study. Eur J Anaesthesiol. 2015;32(1):37–43. https://doi.org/10.1097/EJA.0000000000000120. (PMID: 25014511).
28. Romano G, Mioni R, Danieli N, et al. Elevated Intrarenal Resistive Index Predicted Faster Renal Function Decline and Long-Term Mortality in Non-Proteinuric Chronic Kidney Disease. J Clin Med. 2022;11(11):2995. https://doi.org/10.3390/jcm11112995. Published 2022 May 25
29. Leodori G, Pellicano C, Gigante A, Rosato E. Estimated glomerular filtration rate and renal resistive index as possible predictive markers of mortality in systemic sclerosis. Eur J Intern Med. 2021;87:83–9. https://doi.org/10.1016/j.ejim.2021.01.025. (Epub 2021 Feb 13 PMID: 33593660).
30. Kosaki K, Tarumi T, Mori S, et al. Cerebral and renal hemodynamics: similarities, differences, and associations with chronic kidney disease and aortic hemodynamics. Hypertens Res. 2022;45(8):1363–72. https://doi.org/10.1038/s41440-022-00944-x.
31. Sistani SS, Alidadi A, Moghadam AA, Mohamadnezhad F, Ghahderijani BH. Comparison of renal arterial resistive index in type 2 diabetic nephropathy stage 0–4. Eur J Transl Myol. 2019;29(4):8364. https://doi.org/10.4081/or.2019.8364.
32. Bigé N, Lévy PP, Callard P, Faintuch JM, Chigot V, Jousselin V, Ronco P, Boffa JJ. Renal arterial resistive index is associated with severe histological changes and poor renal outcome during chronic kidney disease. BMC Nephrol. 2012;25(13):139. https://doi.org/10.1186/1471-2369-13-139. PMID:23098365;PMCID:PMC3531254.
33. Parolini C, Noce A, Staffolani E, Giarrizzo GF, Costanzi S, Splendiani G. Renal resistive index and long-term outcome in chronic nephropathies. Radiology. 2009;252(3):888–96. https://doi.org/10.1148/radiol.2523080351. Epub 2009 Jun 15. 19528356.
34. Barone R, Goffredo G, Di Terlizzi V, et al. Renal resistance index independently predicts worsening of renal function after coronary angiography. Int J Cardiovasc Imaging. 2023;39(1):43–50. https://doi.org/10.1007/s10554-022-02694-w.
35. Yamaguchi Y, Akagaki F, Nakamori A, Sugiura T. Chronological renal resistive index increases related to atherosclerotic factors, and effect of renin-angiotensin system inhibitors. Clin Exp Nephrol. 2019;23(4):513–20. https://doi.org/10.1007/s10157-018-1667-y. (Epub 2018 Nov 13 PMID: 30426291).
36. Leoncini G, Martinoli C, Viazzi F, et al. Changes in renal resistive index and urinary albumin excretion in hypertensive patients under long-term treatment with lisinopril or nifedipine GITS. Nephron. 2002;90(2):169–73. https://doi.org/10.1159/000049038.
37. Nistor I, De Sutter J, Drechsler C, et al. Effect of renin-angiotensin-aldosterone system blockade in adults with diabetes mellitus and advanced chronic kidney disease not on dialysis: a systematic review and meta-analysis. Nephrol Dial Transplant. 2018;33(1):12–22. https://doi.org/10.1093/ndt/gfx072.
38. de Borst MH, Navis G. Sodium intake, RAAS-blockade and progressive renal disease. Pharmacol Res. 2016;107:344–51. https://doi.org/10.1016/j.phrs.2016.03.037.

Publisher's Note