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Increase of renal resistive index and mineral metabolism disorder in patients with acute coronary syndrome with preserved renal function

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Abstract. – OBJECTIVE: Coronary artery disease is one of the first causes of death in the Western world; for this reason, it is essential to identify new, systemic, non-invasive and low-cost cardiovascular risk markers. The acute coronary syndrome includes ST-Elevation Myocardial Infarction (STEMI) and Non-ST-Elevation Myocardial Infarction (NSTEMI), based on ECG findings. We aimed to evaluate Renal Resistive Index (RRI) as a marker of cardiovascular risk and assess the associations with other cardiovascular risk factors (metabolic indexes, mineral metabolism disorders and endothelial dysfunction and atherosclerosis markers) in STEMI and NSTEMI patients.

PATIENTS AND METHODS: Clinical, laboratory and instrumental examinations as metabolic and inflammation indexes, markers of atherosclerosis and endothelial dysfunction (renal function, mineral metabolism disorders, inflammation indexes, Intima Media Thickness (IMT), Ankle Brachial Pressure Index, Left Ventricular Mass Index, Relative Wall Thickness) were performed.

RESULTS: Eighty-one patients with STEMI and NSTEMI were enrolled. We showed a significant positive correlation between RRI and age ($p<0.01$), intact parathyroid hormone ($p<0.01$) and IMT ($p<0.01$), as well as a significant negative correlation between RRI and body surface area (BSA) ($p=0.02$), estimated Glomerular Filtration Rate (eGFR) ($p<0.01$), serum calcium ($p<0.01$) and 25-hydroxy-vitamin D ($p=0.03$). Moreover, we found a significant correlation between RRI and male patients ($p<0.01$), coronary artery disease history (CAD) ($p=0.049$), hypertension ($p=0.025$) and left ventricular eccentric hypertrophy (LVEH) ($p=0.047$).

CONCLUSIONS: Our study showed an association between RRI and the main traditional and non-traditional cardiovascular risk factors involved in atherosclerosis pathogenesis, such as age, BSA, hypertension, male sex, CAD history, mineral metabolism disorders and LVEH, in patients with preserved renal function. Moreover, we found a significant correlation between RRI and eGFR, suggesting that RRI could be useful in the evaluation of both renal function and progression of renal damage, even in an early stage with a conserved or only slightly reduced kidney function. We also showed a significant correlation with some markers of systemic atherosclerosis such as IMT and LVEH. For a more precise assessment of prognosis and cardiovascular risk in patients with high cardiovascular mortality, we suggest performing a systematic RRI evaluation, considering the non-invasive nature of the procedure, its reproducibility, easy execution, and low costs.

Key Words:
Cardiovascular disease, Estimated glomerular filtration rate, Mineral metabolism, Renal resistive index.

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Introduction

Cardiovascular disease (CVD) is still the first cause of death worldwide, with 17.7 million deaths, most of them are due to heart attack and stroke[1]. Therefore, it is essential to identify new, systemic, non-invasive and low-cost cardiovascular risk markers[2,3]. The prognosis after an acute coronary syndrome (ACS) depends not only on the extension of the myocardial damage, but also on the cardiovascular risk factors and patients' comorbidity[4,5]. Renal resistive index (RRI) measured using Doppler ultrasonography may be considered a marker of systemic atherosclerosis. It has been described a correlation between increased value of RRI and cardiovascular events and mortality, even if only in patients with renal failure[6]. Originally, Resistive Index (RI) has been proposed by Pourcelot as stated by Rivers et al[7] to define the resistance of blood flow in peripheral arteries, but right now, RRI is widely considered as a marker of both a renal and systemic vascular damage[8-10]. Moreover, RRI appears to increase in many systemic diseases, such as diabetes, essential hypertension, obesity and hyperparathyroidism[11,12]. Many studies showed that patients with disorders of mineral metabolism have an increase in cardiovascular disease[13]. Many reports[14-16] showed that hyperparathyroidism and vitamin D deficiency may induce endothelial dysfunction and vascular calcifications with an increased cardiovascular risk. However, no study has shown an association between mineral metabolism disorders, RRI and cardiovascular risk in patients with preserved kidney function.

The aim is to evaluate RRI as a novel cardiovascular risk marker associated with traditional and non-traditional risk factors, as metabolic indexes, mineral metabolism disorders and atherosclerosis, and endothelial dysfunction markers in ST-Elevation Myocardial Infarction (STEMI) and Non-STEMI (NSTEMI) patients.

Patients and Methods

The protocol of our study was approved by the Ethics Committee of the Sapienza University of Rome, Italy. We obtained written consent from all enrolled patients and the study complies with the principles of the Helsinki Declaration. In this observational study, from October 2016 and June 2018, we enrolled 81 patients, 61 males and 20 females from 40 to 80 years (mean age 62 ± 7.6 years), with ACS. According to ACS diagnosis, the patients have been divided into two subgroups, STEMI and NSTEMI. All patients were followed for 6 months after the acute ischemic event.

The inclusion criteria were age from 18 to 80 years and ACS STEMI or NSTEMI.

The exclusion criteria were history of pyelonephritis, renal artery stenosis, obstructive renal failure, intra-abdominal hypertension, arrhythmia, nephroangiosclerosis and estimated glomerular filtration rate (eGFR) < 50 ml/min, calculated with the Chronic Kidney Disease-Epidemiology formula (CKD-EPI)[17].

Renal Resistive Index (RRI)

All patients carried out RRI assessment. Participants were studied with the ultrasound machine Toshiba Aplio xV (Toshiba Aplio xV, Toshiba American Medical Systems, Inc., Tustin, CA, USA) with a 3-3.5 MHz convex transducer[18]. All measurements were made by a single, blinded, experienced ultrasonographer. We used an anterior approach, in the prone position, and an oblique approach, in a lateral position to detect and to sample the renal arteries and intra-parenchymal vessels in both kidneys[19]. Transverse and longitudinal scans were obtained to study the renal parenchyma. The interlobular, interlobar or arcuate arteries in both kidneys were identified by color-flow imaging and blood-flow profile in the artery was monitored by spectral analysis. The average RRI value for each patient was calculated by the mean of RRI in both kidneys. In each patient, we determined the peak systolic velocity and end-diastolic velocity (centimeters/second) to calculate the renal resistive index (RRI) as = (1 – [end-diastolic velocity ÷ maximal systolic velocity]) × 100. RRI values were determined with the mean of 3 separate measurements in the superior renal pole, interpolar regional, and inferior pole in both kidneys. Three to five reproducible and consecutive waveforms with similar aspects from each kidney are obtained. These measurements were used to calculate the average RRI value for each kidney, and then the average RRI value for each patient was calculated as the mean of the RRI in the left and right kidneys.

Laboratory

Venous blood sampling was performed after a 12-hour fast. In all patients hemoglobin (g/dl), serum glucose (mg/dl), serum insulin (μU/ml), to-

tal serum cholesterol (mg/dl), serum triglycerides (mg/dl), high-density lipoprotein (HDL) (mg/dl), low-density lipoprotein (LDL) (mg/dl), serum creatinine (mg/dl), serum nitrogen (mg/dl), serum uric acid (SUA) (mg/dl), serum calcium (mg/dl), serum phosphorus (mg/dl), serum electrolytes (mEq/l), homocysteinemia (mmol/l), C-reactive protein (CRP) (mg/dl), erythrocyte sedimentation rate (ESR) (mm), were measured by standard techniques. 25-hydroxy-vitamin D (25-OH-Vit D) (ng/ml), intact parathyroid hormone (iPTH) (pg/ml) was measured by radioimmunoassay. N-terminal pro-B-type natriuretic peptide (NT-proBNP) (pg/dl) was measured using automated analyzer Elecsys®2010 (Roche Elecsys 2010 chemistry analyzer, Cobas Integra 400 PlusAnalyzer, Geislingen, Germany). Insulin resistance was assessed using the homeostasis model assessment (HOMA-IR)[20].

Anthropometric Assessment

Body weight was determined to the nearest 0.1 kg using a calibrated digital scale. Body mass index (BMI) was calculated from a person's weight and height (weight (kg)/height $(m)^2$).

Blood Pressure Measurements

Clinic Blood Pressure (BP) measurements were performed three times after 10 minutes of rest in a seated position using a standard sphygmomanometer and cuffs adapted to the arm's circumference, as per British Hypertension Society guidelines. The systolic and diastolic BP levels were assessed using the appearance and disappearance of Korotkoff sounds. Hypertension was defined as systolic BP $\geq$ 140 mmHg or diastolic BP $\geq$ 85 mmHg on repeated measurements. We determined the ankle/brachial pressure index (ABPI), the measurement of the ratio of the Systolic BP in the ankle and in the arm (normal values 0.9-1).

Carotid Intima-Media Thickness Assessment

Common carotid artery imaging was performed with B-mode ultrasound machine Toshiba Aplio xV (Toshiba Aplio xV; Toshiba American Medical Systems, Inc., Tustin, CA, USA) equipped with a 5- to 12-MHz linear transducer with a 0.01-mm resolution, following a standardized vascular protocol. Intima-media thickness (IMT) was sampled in three sites, right and left side: internal carotid artery, carotid bulb and common carotid artery. Images were captured in end-diastole triggered by electrocardiographic recording. The mean value was calculated and considered normal between 0.55 and 0.9 mm.

Echocardiography

All patients underwent an echocardiographic examination to assess the morphology and functionality of the heart. We used a Philips model iE33 equipped with the S5-1 transducer. We evaluated the interventricular septal thickness as well as the posterior wall thickness at end-diastole (n.r. male 0.6-1 cm; female 0.6-0.9 cm,) and the end-diastolic left ventricular (LV) dimension in M-mode and in the parasternal long axis (n.r. 42-58.4 mm for male and 37.8-52.2 mm for female). The following parameters were assessed: left ventricular mass index and the relative wall thickness, the presence of concentric or eccentric hypertrophy and the presence of diastolic dysfunction. In addition, we evaluated the end-systolic and diastolic volume (63-150 ml and 21-61 ml for male, 46-106 ml and 14-42 ml for female), using Simpson's biplane method to estimate the ejection fraction (52-72% for male and 54-74% for female). We also calculated the tricuspidal annular plane systolic excursion to estimate the systolic function of the right ventricle (abnormality threshold <17 mm).

Statistical Analysis

Data's statistical analysis was performed using STATA version 13.1. software. We used "Skewness and Kurtosis test for normality" for the continuous variable to evaluate the range of normality and apply proper test. Variables are expressed as median and range; "Spearman's ρ test" was used to assess all correlations. Categorical variables are expressed as absolute frequency and percentage; we used "Mann Whitney U test" for all correlations with them. A probability value of $p<0.05$ was considered to be statistically significant. We also used "Bonferroni adjusted p-value" to consider multiple comparisons.

Results

Patients' characteristics are shown in Table I and Table II. In summary, we enrolled 81 patients (20 females) with a mean age of 62 (40; 92) years, of which 22 patients (27.2% of our cohort) had an ACS-STEMI, while 59 patients

Table I. Patients' characteristics: quantitative parameters.

Parameter	Median	Range (min-max)
AGE	62	40-92
BMI	26.0	16.6-39.8
BSA	1.85	1.33-2.24
PTCA	1	0-9
Creatinine	0.9	0.6-1.5
eGFR (CKD-EPI)	83	51-130
eGFR (MDRD)	85	53-137
Serum uric acid	5.55	3.19-10.8
Serum calcium	8.8	2.3-10.22
Serum phosphorus	3.3	0.6-5.8
Serum sodium	140	109-148
Serum potassium	4.12	3.14-5.2
CRP	17000	1000-252000
25-OH-Vit D	13	3-70
iPTH	56	15.2-270.6
IMT	1.05	0.66-1.5
RRI	0.71	0.56-1.00

Abbreviations: BMI, Body mass Index; BSA, Body Surface Area; CRP, C Reactive Protein; eGFR, estimated Glomerular Filtration rate, 25-OH-Vit D, 25-hydroxy-vitamin D; iPTH, intact parathyroid hormone; IMT, Intima Media Thickness; RRI, Renal Resistive Index.

(72.8%) had a ACS-NSTEMI. All the participants showed preserved or slightly reduced renal function (Table I) with median eGFR values (based on Modification Diet of Renal Disease (MDRD) and CKD-EPI) (ml/min/1.73 m^2) of 85 (53; 137) and 83 (47; 130) and with a BMI (kg/m^2) of 26.0 (16.6; 39.8) (Table I) and Body Surface Area (BSA) (m^2) of 1.85 (1.33; 2.24). Twenty-seven patients (33.3% of our cohort) were affected by diabetes, 55 (67.9%) by arterial hypertension, 39 (48.2%) by dyslipidemia; 58 patients (71.6%) were smokers and 20 patients (24.7%) were obese; 27 patients had in anamnesis a familiarity for CVD (33.3%) and only 10 patients had a Coronary artery disease history (CAD) (12.4%) (Table II). Moreover, 33 patients (54.1% of our cohort) showed LV normal geometry, while 5 patients (8.2%) presented a LV

Table II. Patients' characteristics: qualitative parameters.

Parameter	N.	Total	%
Sex – Male	61	81	75.3
Sex – Female	20	81	24.7
Diabetes	27	81	33.3
Hypertension	55	81	67.9
Dyslipidemia	39	81	48.2
Smoker	58	81	71.6
Familiarity with CVD	27	81	33.3
Obesity	20	81	24.7
CAD history	10	81	12.4
Death	3	81	3.7
LV normal geometry	33	61	54.1
LV concentric hypertrophy	5	61	8.2
LV concentric remodelling	13	61	21.3
LV eccentric hypertrophy	10	61	16.4
STEMI	22	81	27.2
NSTEMI	59	81	72.8
CRP (>5000)	65	81	80.3

Abbreviations: CAD, Coronary artery disease; CRP, C Reactive Protein; CVD, Cardiovascular disease; LV, Left Ventricular; STEMI, ST-Elevation Myocardial Infarction; NSTEMI, Non-ST-Elevation Myocardial Infarction.

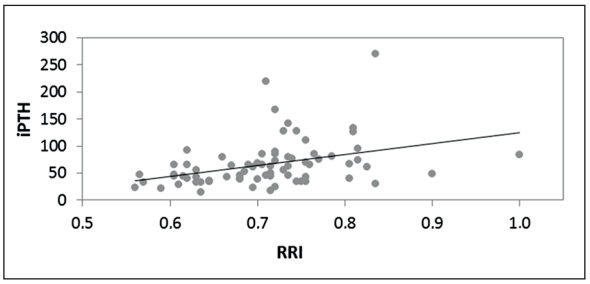

Figure 1. Significant positive correlation between RRI and iPTH (r= 0.4514; p<0.001). *Abbreviations*: iPTH, intact parathyroid hormone; RRI, renal resistive index.

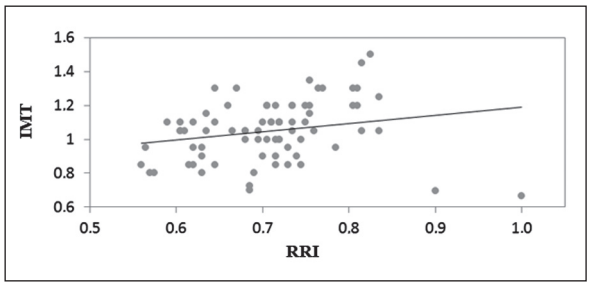

Figure 2. Significant positive correlation between RRI and IMT (r= 0.3516; p<0.001). *Abbreviations*: IMT, Intima Media Thickness; RRI, renal resistive index.

concentric hypertrophy, 13 patients (21.3%) a LV concentric remodeling and 10 (16.4%) a LV eccentric hypertrophy (Table II). In our study, we found significant positive correlations between RRI and age (r=0.584, p<0.001); moreover, we found an increased value of RRI in patients with high levels of iPTH (r=0.451, p <0.001) and IMT (r=0.351, p<0.001) (Figure 1, Figure 2). On the contrary, a significant negative correlations was found between RRI and eGFR (CKD-EPI: r= -0.522, p<0.001, MDRD: r= -0.453, p<0.001) (Table III) and also between RRI and serum calcium (r= -0.370, p<0.001) as well as 25-OH-Vit D (r= -0.259, p=0.03) and BSA (r= -0.270, p=0.016) (Table III, Figure 3). Moreover, we found a significant correlation between RRI and male patients (p<0.001), CAD history (p=0.049), hypertension (p=0.02) and left ventricular eccentric hypertrophy (LVEH) (p=0.047) (Table IV, Figure 4). We did not observe significant differences between the STEMI and NSTEMI subgroups.

Discussion

This study showed a significant correlation between RRI and some important traditional and non-traditional cardiovascular risk factors, such as age, BSA, CAD history, hypertension, LVEH and mineral metabolism disorders. RRI is used to evaluate vascular and parenchymal renal abnormalities, but according to many studies[21,22], it is now considered a systemic vascular

Table III. Correlations between RRI and quantitative parameters.

Parameter	Median	Range (min-max)
Age	**0.584**	**< 0.001**
BMI	-0.091	0.426
BSA	**-0.270**	**0.016**
PTCA	0.028	0.806
Creatinine	0.260	**0.021**
eGFR CKD-EPI	-0.522	**< 0.001**
eGFR MDRD	-0.453	**< 0.001**
Serum uric acid	0.044	0.706
Serum calcium	-0.370	**< 0.001**
Serum phosphorus	0.014	0.900
Serum sodium	0.043	0.706
Serum potassium	0.117	0.304
CRP	0.172	0.130
25-OH-Vit D	-0.259	**0.025**
iPTH	0.451	**< 0.001**
IMT	0.351	**< 0.001**

Abbreviations: BMI, Body Mass Index; BSA, Body surface area, PTCA, percutaneous transluminal coronary angioplasty, eGFR, estimated Glomerular Filtration rate; CRP, C Reactive Protein; 25-OH-Vit D, 25-hydroxy-vitamin D; iPTH, intact parathyroid hormone; IMT, Intima Media Thickness.

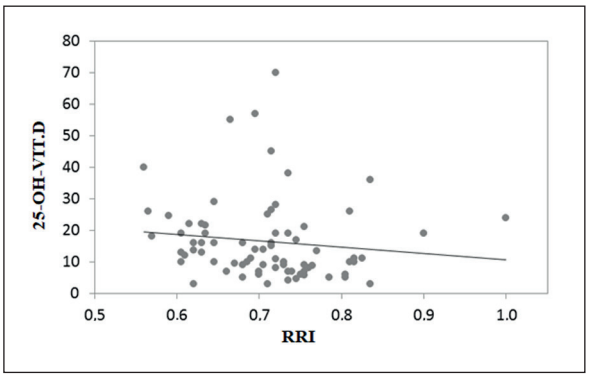

Figure 3. Significant negative correlation between RRI and 25-OH-Vit D (r= -0.259; *p*=0.03). *Abbreviations:* 25-OH-Vit D, 25-hydroxy-vitamin D; RRI, renal resistive index.

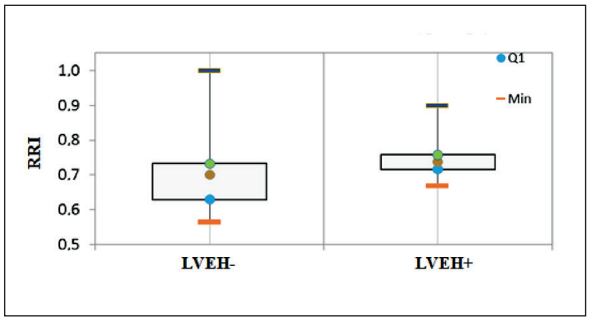

Figure 4. Significant correlation between RRI and LVEH (Mann-Whitney *p* =0.047). *Abbreviations*: LVEH, Left Ventricular Eccentric Hypertrophy; RRI, renal resistive index.

marker. RRI is influenced by renal and extra-renal factors, such as renal vascular resistance and compliance, renal interstitial and venous pressure, heart rate, tachy-brady arrhythmias, aortic and vascular rigidity, severe hypotension, pulse pressure and perirenal or subcapsular fluid. Hence RRI should not be considered only as a marker of renal disease. As assessed in our study, Boddi et al[21] showed a correlation between RRI and hypertension, suggesting that a higher RRI could detect renal organ damage, due to hypertension and diabetes, precociously when renal function is yet preserved. The association between RRI and eGFR is a discussed topic in literature, also because both values can be influenced by age. Despite the presence of an elderly population in our sample, the eGFR remained within a normal range, such as RRI. Therefore, our data seem to confirm this association and the predictive value with a better evaluation of renal damage of RRI, in particular in early stage in patients with preserved renal function. As a matter of fact, RRI reflects the impairment of intrarenal hemodynamics that cannot be adequately elucidated by eGFR alone. Therefore, the assessment of RRI could be useful in prognostic evaluation of patients with CVD[22,23]. Doi et al[11] showed a correlation between RRI and renal function in hypertensive patients, reporting that a high RRI is associated with an increased risk of cardiovascular and renal outcomes, and the combination of high RRI and low eGFR is a powerful predictor of these diseases in essential hypertension. As previously explained, in CKD patients with hypertension, RRI evaluation could integrate predictors of cardiovascular and renal outcomes. Bigé et al[24] reported that a high RRI is associated with severe interstitial fibrosis, arteriosclerosis and renal function decline, suggesting that RRI could contribute to identify patients at high risk of progression of renal damage and who may benefit from nephroprotective treatments. This association between RRI and cardiovascular and renal risk is not completely clear but some pathogenetic hypotheses exist. Previous histological studies[25-27] have demonstrated that RRI correlates with renal function and with renal atherosclerosis or tubule-interstitial damage. In renal allograft patients, RRI in transplanted kidneys significantly correlates

Table IV. Correlations between RRI and qualitative parameters.

Parameters	Mann-Whitney *p*-value
Sex	**0.008**
Diabetes mellitus	0.493
Hypertension	**0.025**
Dyslipidemia	0.415
Smoker	0.110
Familiarity with CVD	0.636
Obesity	0.814
CAD history	**0.049**
Death	0.420
LV normal geometry	0.130
LV concentric hypertrophy	0.926
LV concentric remodelling	0.915
LV eccentric hypertrophy	**0.046**
STEMI	0.567
PCR (> 5000)	0.555

Abbreviations: CVD, Cardiovascular Disease; CAD, Coronary artery disease; LV, Left Ventricular; STEMI, ST-Elevation Myocardial Infarction; NSTEMI, Non-ST-Elevation Myocardial Infarction; CRP, C Reactive Protein.

with the recipient's age but not with the age of the kidney itself, suggesting that extra-renal factors, such as vascular stiffness, could have a major effect on renal Doppler indexes[28]. Vascular resistance and compliance, which represent the ability of a blood vessel wall to expand and contract passively with changes in pressure, are the main predictors of RRI. Other studies showed the association between RRI and CVD parameters with a significant correlation between RRI and ABPI and carotid-femoral pulse wave velocity[29]. Other studies showed an association between RRI and arterial/aortic stiffness index and central pulse pressure in hypertensive patients[30]. Therefore, RRI could be considered a marker of systemic atherosclerotic rather than a specific marker of renal damage[30]. In our research, we did not find an association between RRI and ABPI, but we showed a significant correlation with IMT, as previously reported by Geraci et al[31], whose study showed a clear association between RRI and the severity of carotid atherosclerosis, suggesting RRI as a possible marker of systemic vascular changes. Moreover, we found a significant correlation between RRI and previous CAD, as already reported by Quisi et al[32]. Their study showed a clear association between the severity of CAD, in NSTEMI patients, and LVEH, as previously reported by Alterini et al[33], suggesting that RRI could be a possible surrogate marker and a predictive index of all-cause mortality. Recently cardiac remodelling has been used to better define cardiac function. Eccentric hypertrophy, caused by the addition of sarcomeres in series, leads to a large, dilated ventricle with partial wall thinning. Cardiac remodelling is commonly defined as a pathological state that may occur after myocardial infarction, pressure or volume overload and idiopathic dilated cardiomyopathy; it is also known that training excessively may lead the heart to develop several myocardial adaptations causing a physiological state of cardiac remodelling. These morphological changes are clinically characterized by cardiac size and shape modifications due to increased load[34]. A new classification of left ventricular geometry based on left ventricular dilatation and concentricity has been recently developed. This classification identifies different subgroups based on systemic hemodynamics, left ventricular function and cardiovascular prognosis. Left ventricular dilatation is associated with subclinical renal damage in hypertension, as reported by Ratto et al[35]. These findings provide a pathophysiological rationale for the unfavorable prognosis in patients with left ventricular dilatation. Ganau et al[36] reported back in 1992 that there is an association between hypertension and cardiac geometric adaptation and it may depend on systemic hemodynamics and ventricular load; in fact, eccentric hypertrophy is associated to both pressure and volume overload. The innovative aspect of our study is the significant correlation between RRI and mineral metabolism disorders, in particular with serum calcium, iPTH and 25-OH-Vit D. According to Adami et al[37], the prevalence of Vitamin D deficiency (<30 ng/ml) in the general population is 65% and it increases (86%) in women over 70. This condition increases not only the risk of osteoporosis but especially of cardiovascular events. Hyperparathyroidism and Vitamin D deficiency are directly involved in LVH. Vitamin D receptors (VDRs) are expressed not only in the classical target organs (bone, parathyroid glands, kidneys and intestine) but also in other non-classical targets, including the arteries, the immune system, endocrine organs, the nervous system and heart, causing an up-regulation of the renin-angiotensin-aldosterone system[38]. Many studies showed that Vitamin D deficiency induces endothelial dysfunction. A meta-analysis conducted by Lupoli et al[39] showed that Vitamin D deficiency may be related to subclinical markers of atherosclerosis, in particular IMT[40] and calcium metabolism, and that it induces artery calcifications[41], a novel risk factor for cardiovascular events[42,43]. Moreover, Trovato el al[44] showed an association between LVH, inflammation, iPTH and RRI, even if we did not find a significant correlation with CRP. Therefore, we found a significant correlation between RRI and the main traditional and non-traditional cardiovascular risk factors that suggest using this parameter for the stratification of cardiovascular risk in a population with high mortality.

The limitations of our study are the limited sample size and the cross-sectional, single-center study. Additional prospective follow-up studies with a larger number of patients are necessary to confirm our results.

Conclusions

This study showed that RRI could be a useful marker for the evaluation of cardiovascular risk, considering the associations with traditional and

non-traditional risk factors and with important atherosclerosis markers, such as IMT and LVEH. Furthermore, the correlation between RRI and eGFR suggests that RRI could be used for a more accurate evaluation of renal function and the progression of renal damage, even in patients with preserved renal function. Considering the non-invasive nature of the procedure, its reproducibility, easy execution and low costs, we suggest a systematic RRI evaluation for a more precise assessment of prognosis and cardiovascular risk in patients with high cardiovascular morbidity and mortality. This study is the first study to show a correlation between RRI and mineral metabolism disorders in patients with preserved kidney function.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Declaration of Interests

The authors alone are responsible for the content and writing of the paper. The authors report no conflicts of interest. The manuscript has been seen and approved by all authors. The manuscript is not under consideration for publication elsewhere. The authors declare to make available all the data of the study. No funding is declared for this article

Authors' Contribution

Study design: Silvia Lai, Adolfo Marco Perrotta, Francesco Barillà, Anna Paola Mittherofer, Riccardo Iorio, Amalia Mariotti. Data collection: Adolfo Maria Perrotta, Riccardo Iorio, Marco Mangiulli. Statistical analysis: Luigina Ferrigno, Adolfo Maria Perrotta, Marco Mangiulli. Data interpretation: Bledian Asllanaj, Silvia Lai, Marco Mangiulli, Amalia Mariotti, Anna Paola Mittherofer. Final revision of the manuscript: Silvia Lai, Adolfo Maria Perrotta, Viola D'Ambrosio, Francesco Barillà.

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