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Role of hypertension in left ventricular morphology among chronic kidney disease patients

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Abstract

Hypertension is a well-established marker of cardiovascular risk in patients with chronic kidney disease (CKD). Also it appears to be the main stimuli for left ventricular hypertrophy (LVH), which is the main manifestation of uremic cardiomyopathy and may contribute to the onset of cardiac complications in uremic patients. The study included a cohort of 130 patients with CKD (eGFR <60ml/min/1.73m^2). They were examined by standard echocardiography and blood chemistry at baseline. We divided them in 4 groups according to CKD stages 3 to 5D, where 5D patients have hemodialysis age < 3months (were included in hemodialysis program for less than 3 months). Overall prevalence of hypertension was 84%, and overall prevalence of LVH was 73%. Concentric hypertrophy was the prevalent type of LVH (55%). Although the number of hypertensive patients in the group with LVH is significantly higher compared to the group of hypertensive patients without LVH (p Chi-χ2 = 0.02), there is no difference between the LVH degree in hypertensive vs. non-hypertensive patients, expressed by mean ± standard deviation of left ventricular mass index (LVMi) (p = 0.631240 Student test - S). Anemia, diastolic dysfunction and LVMi were the most important risk factors for CKD progresion (p<0.0001). The fact that LVH was concentric in the majority of patients shows that pressure overload is main factor for increased LVMi in early stages of CKD. Hypertension is a modifiable risk factor for LVH so we must try to prevent cardiac remodeling by controlling blood pressure.

Keywords: left ventricular hypertrophy, arterial hypertension, end-stage renal disease, chronic kidney disease, anemia, cardiovascular risk

Introduction

CKD is defined by structural abnormalities of kidney, or renal function that are present for more than 3 months with a resounding impact on health [1].

Estimated prevalence of CKD in the U.S. population is 13.1% by 2005-2010 NHANES study [2]. In Australia the incidence of CKD is 101 cases per 1 million persons / year [3].

CKD patients have an increased risk of cardiovascular morbidity and mortality of 20-30 times greater than that of a similar individual without renal impairment [4].

Left ventricular hypertrophy (LVH) is the main manifestation of uremic cardiomyopathy, encountered in 70% - 80% of incident dialysis patients and may contribute to the onset of extensive cardiovascular diseases in chronic kidney disease

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(CKD) patients [5]. These alterations result from the chronic pressure and volume overload, in association with numerous other metabolic and neurohumoral abnormalities, and with vascular damage as calcifications, arteriosclerosis and increased arterial stiffness [6].

Hypertension (HTN) is the most prevalent cardiovascular long-term condition to be associated with a high rate of multimorbidity [7]. Also, hypertension and arterial stiffness, two factors imposing a high afterload to cardiac work, are the main causal risk factors for LVH in CKD patients [8, 9].

We aimed to evaluate several cardiovascular risk factors in CKD patients. We analyzed prevalence and type of LVH, prevalence and role of anemia, diastolic dysfunction, age, body surface area (BSA) and albuminuria as risk factors for CKD progression.

Also we calculated the risk of cardiovascular events for 10 years, accounted stroke or heart failure using QRISK2-2014 and highlighted its relationship with major cardiovascular risk factors.

Materials and methods

We conducted a retrospective study that included a cohort of 130 patients with CKD (eGFR <60ml/min/1.73m^2) all of them admitted in Nephrology Department of Clinical Emergency County Hospital Craiova between 1 January 2010 and 1 June 2014. Patients with atrial fibrillation, left ventricular failure, severe systolic left ventricular dysfunction (ejection fraction less than 50%) were excluded from the study. All pa-

Table 1. Correlations of QRISK2 with several cardiovascular risk factors.

	Stage 3 CKD n=28	Stage 4 CKD n=30	Stage 5 CKD n=27	Stage 5D CKD n=45	P
Age (years)	60.3±12.2	60.7±13.6	57.9±16.4	56±22	0.63
Women (%)	8(29)	10(33)	12(44)	25(56)	0.09
HTN (%)	24(85)	24(80)	27(100)	33(73)	0.03
SBP (mmHg)	139.3±10.9	143.2±11.6	152.8±6.7	146.5±21.2	0.009
DBP (mmHg)	69.1±6.7	75±6.9	78.4±4.1	73.6±12.8	0.003
Diabetes (%)	16(57)	11(36)	2(7)	8(17)	0.0001
Hb (g/dl)	12.1±1.3	9.7±1.2	10.2±1.4	9.5±0.9	<0.0001
eGFR (ml/min/1.73m^2)	42.6±8	20.5±4.3	14.5±1.2	7.6±1	<0.0001
Uric acid (mg/dl)	6.31±1.41	6.97±1.79	7.55±1.72	8.09±6.13	0.001
C reactive protein (mg/dl)	1.16±1.30	1.33±1.87	2.85±2.46	3.53±2.17	<0.0001
Proteinuria (mg/24h)	45.61±25.01	153.72±139.07	250.24±241.54	490.57±368.06	<0.0001
IVS (mm)	13.1±1.9	12.9±1.9	13.5±1.7	13.2±1.7	0.64
PWT (mm)	11.7±1.6	12.5±1.8	12.8±1.8	13.9±2.3	0.0001
LVEDD (mm)	46±4.2	50.1±7.4	52.2±6.5	47±5.3	<0.0001
LVESD (mm)	34.3±6	38.7±10.1	41.8±7.2	34.2±3.9	<0.0001
LVMi (g/m^2)	119±23.1	165.1±56.1	198.1±64.6	248.6±126.5	<0.0001
LVH (%)	12(42)	21(70)	25(92)	37(82)	0.0001
mitral E velocity(m/s)	0.63±0.18	0.66±0.17	0.69±0.12	0.60±0.20	0.15
mitral A velocity (m/s)	0.65±0.12	0.69±0.11	0.76±0.15	0.79±0.09	<0.0001

HTN-hypertension, SBP-systolic blood pressure, DBP-diastolic blood pressure, Hb-hemoglobin, eGFR-estimated glomerular filtration rate, IVS- interventricular septum, PWT-posterior wall thickness, LVEDD-left ventricle end-diastolic diameter, LVESD-left ventricle end-systolic diameter, LVMi-left ventricle mass index, LVH-left ventricle hypertrophy

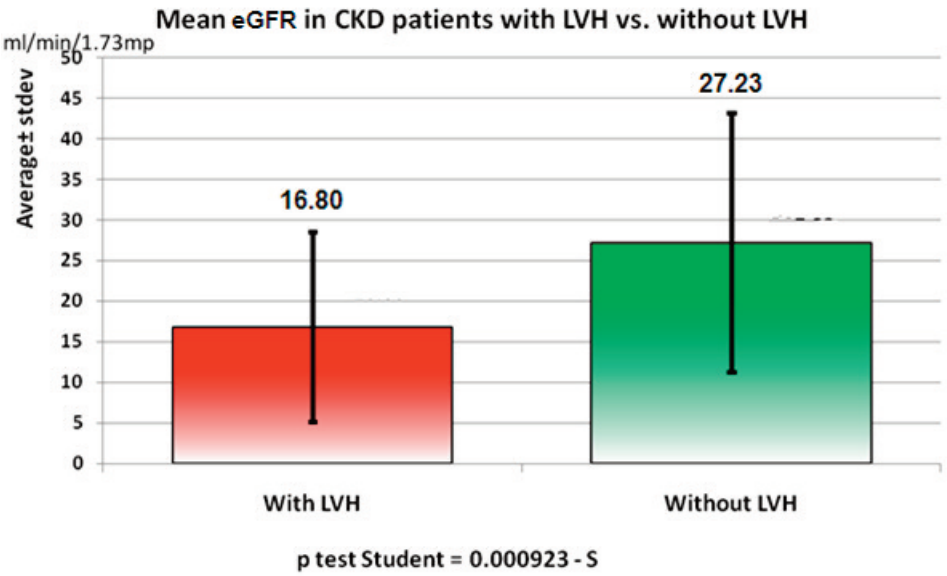

Figure 1. Comparison of mean eGFR in CKD patients with LVH vs. without LVH.

tients were examined by standard echocardiography and blood chemistry at baseline. Left ventricular end-diastolic, systolic dimensions, end-diastolic, and systolic wall thickness of the interventricular septum and left ventricular wall were determined using standard echocardiographic 2-D and M-mode measurements. LVMi was measured according to the ASE guidelines [10], and was defined as LVMi >130 g/m in males, and LVMi >112 g/m in females. Mitral inflow velocity was traced and the following variables were derived: peak early (E) and late (A) transmitral flow velocities and the ratio of early to late peak velocities (E/A). We divided them in 4 groups based on eGRF according to CKD stages 3 to 5D, where 5D patients have hemodialysis age < 3months. The eGFR was calculated by CKD-Epi equation according to KDIGO 2013 guidelines. For statistical analysis we used Kruskall-Wallis for non-parametric data, t-Sudent for unequal variances, Corelation and Multiple regression analysis. All values are expressed as mean ± standard deviation unless stated otherwise in the text.

Results

From a demographic perspective our group consisted of 55 women and 75 men with a mean age 58.46 years, and the mean eGFR was 19.60 ml/min/1.73m^2 (±13.72 ml/min/1.73m^2). Baseline characteristics of our cohort can be found in Table 1. There were no statistically significant differences regarding age, gender, or the thickness of the IVS. On the other hand average value of posterior wall thickness

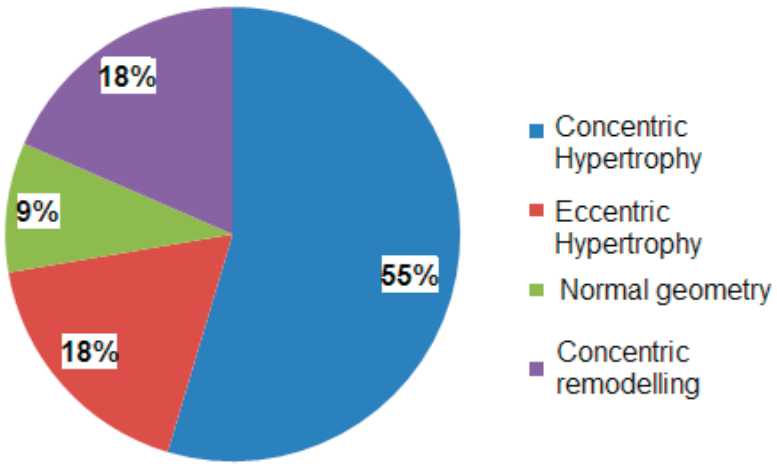

Figure 2. LV morphology in study group.

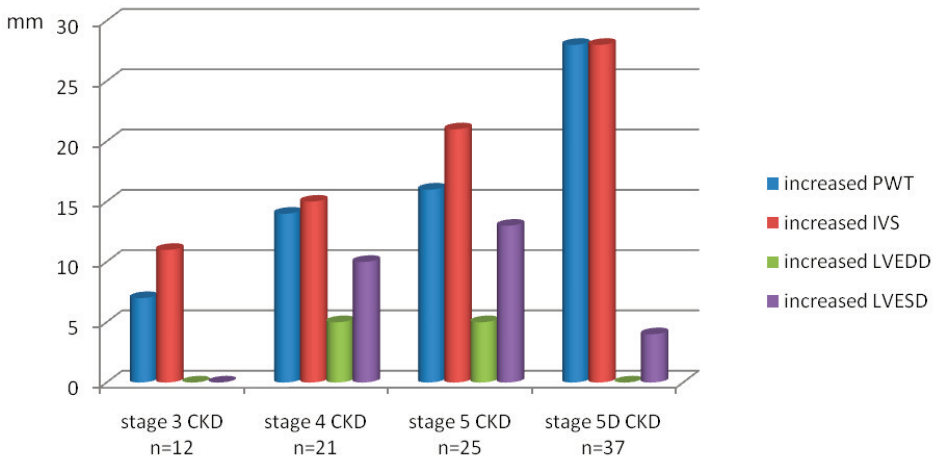

Figure 3. Changes in echocardiographic parameters in patients with LVH.

(PWT), left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), anemia, and LVMi increased with in parallel with the severity of kidney dysfunction. Hypertension was also more frequent in the late stages of CKD (Table 1).

Overall prevalence of LVH was 73% and renal function (estimated by eGFR mean) was worse in CKD patients with LVH vs. CKD patients with no LVH (p test Student = 0.000923 - S) (Fig 1).

Concentric hypertrophy was the prevalent type of LVH in our study (74%) (Fig 2) and was due more to increased PWT and IVS than global enlargement of left ventricle (Fig 3).

Although the number of hypertensive patients in the group with LVH is significantly higher as in the group of hypertensive patients without LVH (p Chi-χ2 = 0.02) (Fig 4), the difference between the LVH degree in hypertensive vs. non-hypertensive patients, expressed by mean ± standard deviation of LVMI, does not reach statistical significance between the two groups (p = 0.631240 Student test - S) (Fig 5).

Multiple regression was performed using eGFR as the dependent variable and LVMi, hemoglobin, diastolic dysfunction, age, body surface area (BSA) and albuminuria as independent variables. Anemia, diastolic dysfunction and LVMi were the most important risk factors for CKD progression (p<0.0001), meanwhile age, BSA and albuminuria had no prognostic value (Table 2).

Diastolic dysfunction was present in 69% patients and correlated directly with eGFR decline (rho Spearman=0.398, p<0.0001) (Fig 6).

We evaluated LVMi prediction power for LVH and HTN with expected, favorable results (Fig. 7 and Fig. 8).

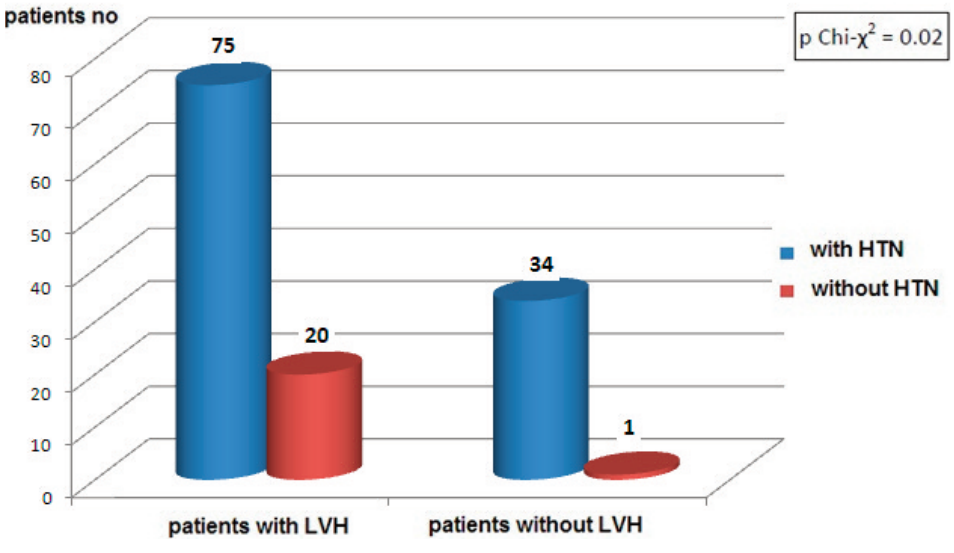

Figure 4. Number of hypertensive patients among LVH and non-LVH groups.

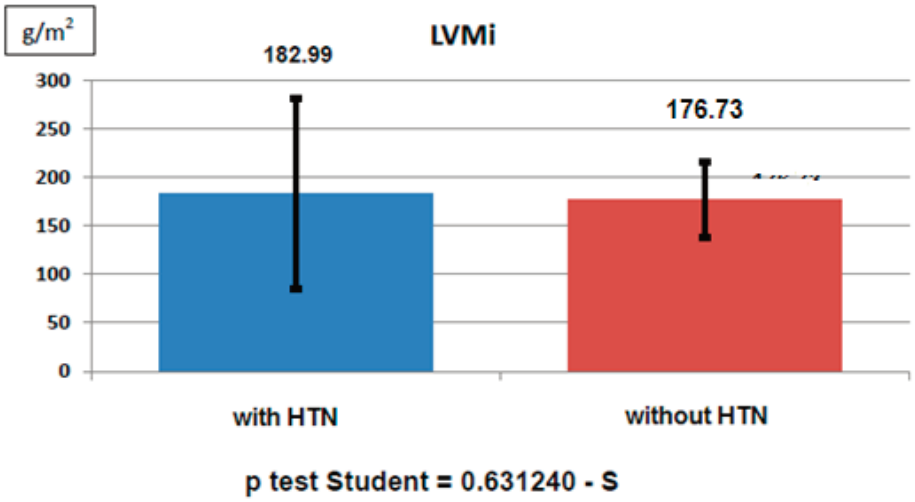

Figure 5. Mean value of LVMi according of presence or absence of HTN.

I've estimated the cardiovascular risk with QRISK2, by age groups and found that cardiovascular risk increases with age (p <0.0001) (Fig 9).

Cardiovascular risk estimated with QRISK2 directly correlated with eGFR (p=0.037), SBP (p=0.001), DBP (p=0.001) and age (p<0.0001) (Table 3).

Medium and increased cardiovascular risk, stratified by CRP, was associated with increased prevalence of LVH (p Chi-χ2=0.001) (Fig 10).

Table 2. Linear regression of risk factors for CKD progression.

	r	p
Hb	0.6146	<0.0001
BSA	0.1667	0.9604
E/A	0.3691	<0.0001
LVMi	-0.4577	<0.0001
24h proteinuria	-0.2129	0.5600
Age	0.08280	0.0758

F-ratio, 26.0676, Significance level, P<0.001, Hb - hemoglobin, BSA - body surface area, E/A - mitral E velocity/mitral A velocity

Discussions

Heart disease in patients with CKD results from a complex interplay between three distinct processes: atherosclerosis, arteriosclerosis, and left ventricular growth and dysfunction [11, 12].

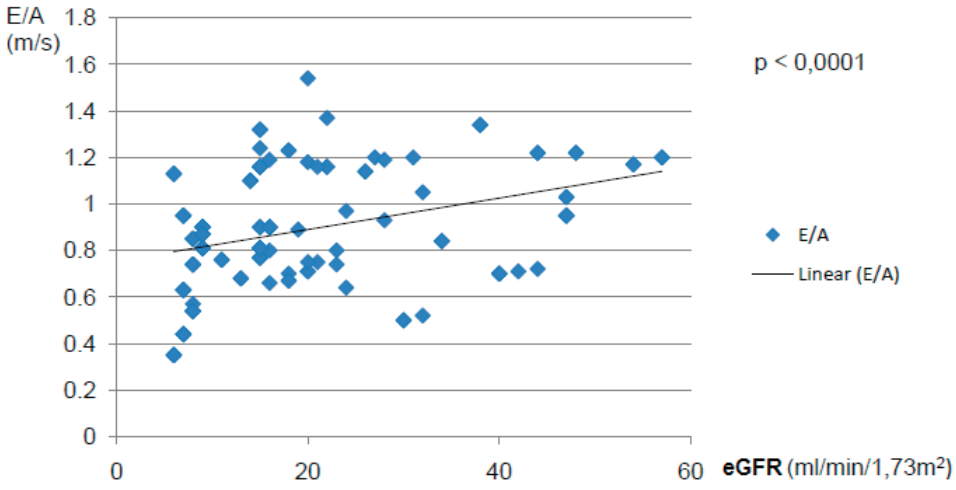

Figure 6. Correlation of diastolic dysfunction with CKD progression.

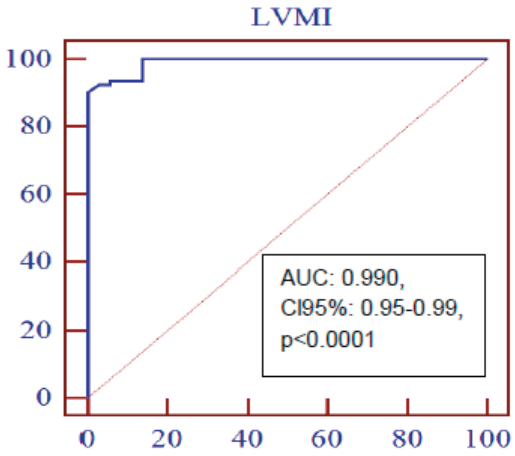

Figure 7. ROC curve for LVMi and LVH.

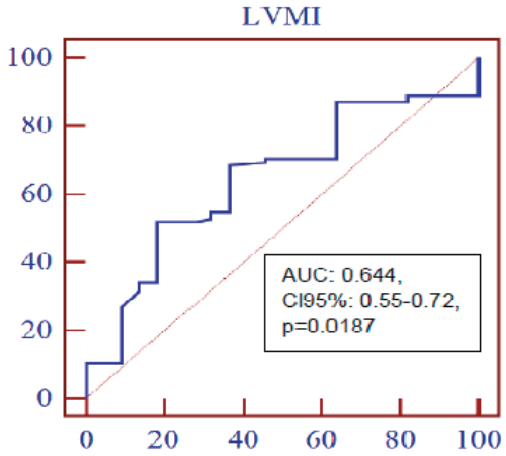

Figure 8. ROC curve for LVMi and HTN.

LVH is the most frequent cardiac alteration in ESRD and is also present in early stages of CKD with a strong predictive power for cardiac morbidity and mortality. LVH was observed in almost 75% of patients at the start of dialysis [13]. In the literature there is a great variability in the prevalence of LVH probably due to the heterogeneity of the populations studied, the use of different methods for estimating glomerular filtration rate (eGFR) or the fact that have been used different values of left ventricular mass in defining LVH. In our study overall prevalence of LVH was 73% determined by using standard echocardiographic 2-D and M-mode measurements of left ventricle in Devereux formula [14]. We found that concentric hypertrophy was the prevalent type of LVH due to chronic pressure overload, findings sustained by an overall prevalence for HTA of 83% and linear correlation with kidney function decline (p=0.03). There was a fairly significant number of patients with concentric remodeling, which is an important predictor of predisposition to impaired LV morphology and appearance of either concentric or eccentric LVH.

However comparing the average value of LVMi among hypertensive patients and those without hypertension didn't

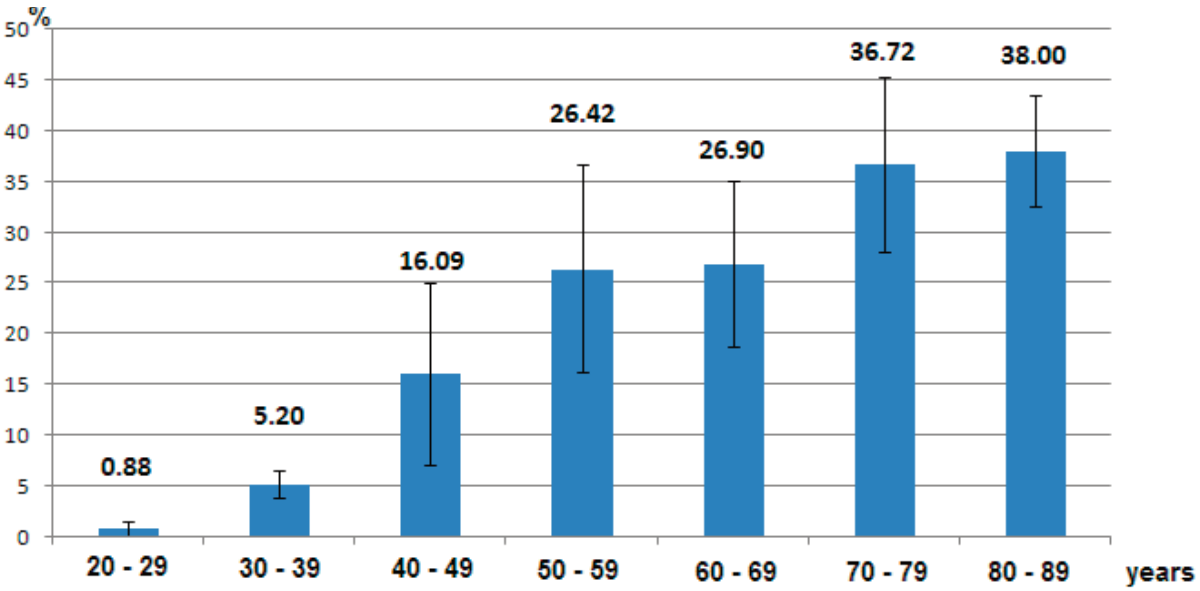

Figure 9. QRISK2 estimate of cardiovascular risk according age distribution.

Table 3. Correlations of QRISK2 with several cardiovascular risk factors.

	r	p
eGFR	0.1831	0.037
SBP	0.2693	0.001
DBP	0.2817	0.001
Age	0.8362	<0.0001
Hb	0.0257	0.771
CRP	-0.0641	0.468

eGFR - estimated glomerular filtration rate, SBP - systolic blood pressure, DBP - diastolic blood pressure, Hb - hemoglobin, CRP - C reactive protein

find statistically significant differences. This can only mean that other co-factors in the etiology of LVH such as loss of elasticity of the blood vessels or the presence of vascular calcification leading to increased pulse pressure were present. LVMi has proved a highly predictive factor for LVH and hypertension.

Using Multiple regression analysis we have shown that anemia is also an independent variable for CKD progression. Diastolic dysfunction is an abnormality of relaxation, filling, or distensibility of the left ventricle that is associated with augmented cardiovascular mortality [15-17]. In our study diastolic dysfunction was highly frequent therefore we can assume that left ventricular diastolic dysfunction is present in all patients with CKD, including those with an early stage of the disease. Also along with LVMi and anemia represents an independent variable for CKD progression ($p<0.0001$).

There are numerous data showing that proteinuria also has prognostic implications as a cardiovascular risk factor [18, 19] but because of other variables in our study it didn't correlate with eGFR. A powerful, independent and graded association exists between the degree of renal albumin loss and cardiovascular risk in many populations including hypertensives, diabetics, those with established vascular disease and the general population [19-21], and therefore is necessary to assess albuminuria levels with standard urinary dipstick testing [22].

We applied the QRISK2 score for patients in our study and found a strong correlation with age and systolic and diastolic blood pressure values. We stratified cardiovascular risk with CRP values according to the AHA/CDC classification and found that medium and increased cardiovascular risk associated with the LVH prevalence. Also, in our study, patients in stages 5 and 5D CKD have an increased cardiovascular risk proving all over again that there is a high morbidity and mortality in the first month to 2 months after starting dialysis [23]. New predictive mortality risk score models are under developement [24] because dialysis is a major medical commitment and clinicians must make more informed decisions about starting hemodialysis [25].

Conclusion

The fact that LVH was concentric in the majority of patients shows that pressure overload is main factor for increased LVMi in early stages of CKD. Anemia is a well-known cardiovascular risk factor in CKD patients and its correction may reduce cardiovascular morbidity and mortality. Even if

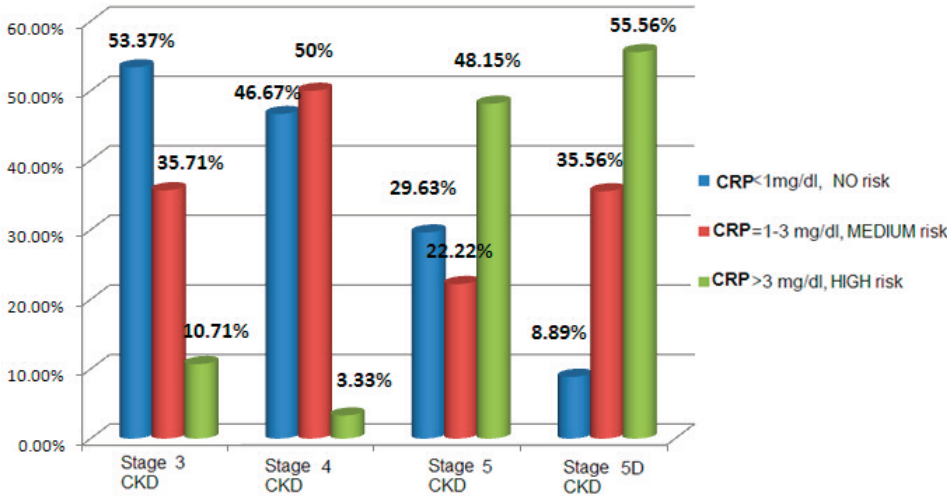

Figure 10. Stratification of cardiovascular risk according to CRP values.

role of albuminuria in CKD is important in predicting cardiovascular risk the fact that it didn't correlate with eGFR in our study means that we may have had other determinants of albuminuria implicated along with renal function decline. In conclusion cardiac echography must be a standard evaluation method in periodic assessment of clinical status in predialysis CKD patients and it's necessary to intervene over modifiable cardiovascular risk factors such as anemia, blood pressure and metabolic unbalances to reduce cardiovascular risk in CKD patients.

Conflicts of interest

The authors of this manuscript certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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