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CARDIOVASCULAR AND NEPHROLOGICAL RISK IN PATIENTS WITH CHRONIC KIDNEY DISEASE IN AMBULATORY CARE

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Ключевые слова: *сердечно-сосудистый риск, хроническая болезнь почек, артериальная гипертензия*

Abstract: Cardiovascular and nephrological risk in patients with chronic kidney disease in ambulatory care. Kuryata O., Semenov V. *Patients with chronic kidney disease (CKD) have higher than in general population all-cause and cardiovascular mortality. Arterial hypertension (HTN) is a powerful potentially modifiable risk factor that affects the majority of patients with chronic kidney disease and one of the main causes of end stage renal disease worldwide. Existing tools for assessment of risk of CKD progression do not take into account arterial hypertension. The aim – to investigate the association between cardiovascular and nephrological risk factors in patients with CKD in ambulatory practice. The study was carried out in the Center of Nephrology Care in Mechnikov Dnipropetrovsk Regional Hospital, Dnipro, Ukraine. 278 patients (114 males and 164 women, aged 41 [31;61] years) with CKD (stages 1-3) who were followed-up in ambulatory care, but required diagnosis or treatment revision were enrolled to the study. All patients were examined and followed-up according to local and European standards. Females slightly prevailed in our study, gender distribution varied insufficiently in groups by CKD progression risk. Elevation of risk of CKD progression was accompanied by rise of prevalence of diabetes mellitus, left ventricle hypertrophy, proteinuria and HTN. Risk of CKD progression correlated with age, systolic and diastolic blood pressure, erythrocyte sedimentation rate, total cholesterol, glomerular filtration rate, albumin excretion rate, duration of HTN and body mass index. Rise of cardiovascular risk was accompanied by rise of proportion of patients with high risk of CKD progression. Increase in risk of CKD progression is associated with rise of burden of cardiovascular risk factors. HTN and blood pressure values should be accounted for assessment of risk of CKD progression.*

Реферат. Серцево-судинний та нефрологічний ризик у пацієнтів з хронічною хворобою нирок в амбулаторній практиці. Курята О., Семенов В. *Пацієнти з хронічною хворобою нирок (ХХН) мають вищу, ніж у загальній популяції, загальну та серцево-судинну смертність. Артеріальна гіпертензія (АГ) є потужним фактором ризику, що піддається модифікації, та зустрічається в переважної більшості пацієнтів з ХХН. АГ є однією з основних причин термінальної ХХН. Наявні інструменти для оцінки ризику прогресії ХХН не враховують АГ. Мета – дослідити асоціацію між кардіоваскулярними та нефрологічними факторами ризику в пацієнтів з ХХН в амбулаторній практиці. Дослідження було проведене в Центрі надання нефрологічної допомоги в КЗ "Дніпропетровська обласна клінічна лікарня ім. І.І. Мечникова", Дніпро, Україна. 278 пацієнтів (114 чоловіків і 164 жінки, віком 41 [31;61] рік) з ХХН (стадії 1-3), що лікувалися амбулаторно, але потребували перегляду діагнозу або лікування в умовах стаціонару, були включені в дослідження. Діагностика та лікування ХХН у всіх пацієнтів проводилася згідно з локальними та Європейськими протоколами. Серед пацієнтів у дослідженні переважали жінки, але гендерний розподіл у групах за ризиком прогресії ХХН не змінювався. Зростання ризику прогресування ХХН супроводжувалося збільшенням частки пацієнтів з цукровим діабетом, гіпертрофією лівого шлуночка та АГ. Ризик прогресування ХХН корелював з віком, систолічним та діастолічним артеріальним тиском, швидкістю зсідання еритроцитів, загальним холестерином, швидкістю клубочкової фільтрації, добовою протеїнурією, тривалістю АГ та індексом маси тіла. Зростання серцево-судинного ризику супроводжувалося збільшенням частки пацієнтів з високи ризиком прогресії ХХН. Збільшення ризику прогресії ХХН асоціюється зі зростанням поширеності факторів ризику серцево-судинних ускладнень. АГ та показники артеріального тиску повинні враховуватися при оцінці ризику прогресії ХХН.*

Patients with chronic kidney disease (CKD) have higher than in general population all-case and cardiovascular mortality (mostly after drop down of glomerular filtration rate (GFR) below 60 ml/min) [4] and proportion of patients who survive to the end stage of renal disease is small [7]. Arterial hypertension (HTN) is extremely common cardiovascular risk factor among patients with CKD [13], but it is still the matter of debate which thresholds and blood pressure (BP) goals should be chosen for patients with CKD [14, 20, 21]. Along with advance of CKD stage, prevalence of HTN increases as well as its resistance to drug therapy [13]. Cut-off points of GFR <60 ml/min and <30 ml/min are used in European guidelines on HTN management and cardiovascular disease prevention to distinct patients of high and very high cardiovascular risk [8, 19, 21]. Urine protein loss >30 mg per 24 hours is considered as a sign of HTN-mediated organ damage [19, 21] and in patients with urine protein loss >300 mg per 24 hours in hypertensive adults is considered as indication for prescription of angiotensin converting enzyme inhibitors or angiotensin receptor blockers [20]. Adverse impact of HTN on CKD course is acknowledged, but neither blood pressure level, nor presence of HTN are accounted in estimation of risk of CKD progression [15, 16]. The aim of the study: to investigate the association between cardiovascular and nephrological risk factors in patients with CKD in ambulatory practice.

MATERIALS AND METHODS OF RESEARCH

The study was carried out in the Center of Nephrology Care in Mechnikov Dnipropetrovsk Regional Hospital, Dnipro, Ukraine. Our aim was to select patients with CKD who were treated ambulatory by primary care physicians (PCPs), but required nephrologist's consultation. From 4540 patients, who were referred to the Center by PCPs in 2017 we selected 278 patients for the analysis who were followed-up in ambulatory care, but required diagnosis or treatment revision. Independent experts provided patient selection in order to exclude patients that required multidisciplinary approach or patients with stable course of CKD. Exclusion criteria: type 1 diabetes mellitus (DM), polycystic renal disease, hereditary renal diseases, operations on kidneys or urinary tract, patients with GFR <30 ml/min. All patients were examined and followed-up according to local and European standards and gave informed written consent on data collection. The study was approved by the Ethics Committee at the Mechnikov Dnipropetrovsk Regional Hospital, Dnipro, Ukraine.

Diagnosis of HTN was based on previous medical records or systolic BP (SBP)≥140 mmHg or diastolic BP≥90 mmHg revealed during examination. Grade of HTN was defined according to 2013 ESH/ESC Guidelines for management of HTN [19]. Cardiovascular risk was assessed according to 2016 European Guidelines on cardiovascular disease prevention in clinical practice [8]. Sokolow-Lyon index was used to detect left ventricle hypertrophy (LVH). Proteinuria was defined as urine albumin excretion >0,03 g/l or protein trace in morning urine void. Risk of CKD progression was assessed according to KDIGO 2012 Clinical Practice Guidelines for the Evaluation and Management of Chronic Kidney Disease [15]. In purpose to classify patients to albuminuria categories we used albumin excretion rate (AER). Body mass index (BMI) was estimated as weight $(kg)/(height (m))^2$. GFR was calculated using CKD-EPI equation [15]. We used estimated pulse wave velocity (ePWV) from age and mean BP as marker of CV diseases [6, 10].

Statistical analysis

Type of data distribution was assessed using Shapiro-Wilk test. As more than 50% of the data were distributed non-parametrically, values were presented as median and interquartile range. Categorical data are presented as n (valid %) to avoid confounding true proportion by missing data. Mann-Whitney and Kruskal-Wallis test were used to compare continuous data, Chi-square test was used to compare categorical data. For correlation analysis we used Spearman's correlation coefficient (ρ). The effect size measurement of linear trend between several groups was performed using Kendall's correlation coefficient (τ). In most cases critical value of p was <0.05. In cases of multiple comparisons we used Bonferroni correction and critical value of p equaled to 0.05/(number of possible comparisons). Data processing and analysis were performed using Libre Office and R [9, 11, 17].

RESULTS AND DISCUSSION

Females were more prevalent in our study, gender distribution varied insufficiently in groups by CKD progression risk (Table 1). Elevation of risk of CKD progression was accompanied by rise of prevalence of DM, LVH, proteinuria and HTN. There were statistically significant differences between groups in age, BMI, duration of HTN, SBP and DBP, ePWV and erythrocyte sedimentation rate (ESR).

Furthermore, we defined statistically significant correlations between CKD progression risk category and following variables: age $(\tau=0.19)$, SBP $(\tau=0.23)$, DBP $(\tau=0.17)$, ESR $(\tau=0.26)$, total cholesterol $(\tau=0.26)$, GFR $(\tau=-0.49)$ and AER $(\tau=0.64, p<0.001$ for all correlations); with duration of HTN $(\tau=0.15, p=0.002)$ and BMI $(\tau=0.12, p=0.007)$.

Clinical characteristics of patients in the study subdivided by risk category of CKD progression

| Parameter	Total	CKD progression risk category				p
		low	moderately increased	high	very high	
		a	b	c	d	
N (valid %)						
Total	278 (100.0)	125 (45.0)	66 (23.7)	54 (19.4)	33 (11.9)	ns
Males	114 (41.0)	53 (42.2)	24 (36.4)	20 (37.0)	17 (51.1)	ns
DM	53 (19.0)	14 (11.2)	16 (24.2)	11 (20.4)	12 (36.4)	ns
LVH	69 (27.6)	24 (20.7)	18 (30.0)	11 (25.6)	16 (51.6)	a-d*
Proteinuria	134 (48.2)	33 (26.4)	35 (53.0)	35 (64.0)	31 (93.9)	a-b, a-c, a-d, b-d, c-d
HTN	204 (73.4)	78 (62.4)	50 (75.8)	45 (83.3)	31 (93.9)	a-c, a-d
Median [interquartile range]						
Age, years	47 [31;61]	38 [25;58]	51 [35;63]	50 [34;66]	53 [41;66]	<0.001
BMI, kg/m^2	26.5 [22.7;30.8]	25.3 [21.5;30.7]	26.7 [23.3;31.4]	27.1 [23.3;29.8]	30.0 [25.5;33.0]	0.015
CKD duration, years	5 [2;16]	5 [2;15]	6 [2;19]	6 [1;14]	5 [1;14]	0.82
AH duration, years	0 [0;10]	0 [0;4]	1 [0;13]	0 [0;10]	5 [0;16]	0.002
SBP, mmHg	130 [120;150]	130 [110;140]	133 [120;146]	132 [118;150]	150 [140;170]	<0.001
DBP, mmHg	85 [75;90]	80 [70;90]	85 [80;90]	85 [80;90]	90 [80;100]	0.003
ePWV, m/s	8.3 [6.5;10.1]	7.0 [6.2;9.1]	9.0 [6.4;10.5]	9.1 [7.3;10.3]	10.2 [7.6;11.6]	<0.001
ESR, mm/h	11 [5;25]	7 [4;15]	12 [5;24]	17 [10;29]	19 [13;35]	<0.001
GFR, ml/min	76.9 [50.4;100.6]	92.0 [76.9;113.2]	80.9 [53.5;98.7]	49.5 [37.7;72.6]	39.1 [33.5;46.5]	<0.001
Total cholesterol, mmol/l	5.3 [4,6;5,9]	4.9 [4.3;5.7]	5.2 [4.6;5.6]	5.5 [5.0;6.2]	5.9 [5.0;8.1]	0.19
AER, mg/24h	0 [0;72]	0 [0;0]	44 [0;69]	85 [0;825]	420 [72;2725]	<0.001

Notes: CKD, chronic kidney disease; DM, diabetes mellitus; LVH, left ventricle hypertrophy; HTN, arterial hypertension; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; ePWV, estimated pulse wave velocity; Hb, hemoglobin; ESR, erythrocyte sedimentation rate; GFR, glomerular filtration rate; AER, albumin excretion rate; * – for p<0.008 for all comparisons of categorical data.

Patients with HTN had similar gender distribution to patients without HTN, but were substantially older (53 [38;64] vs 29 [23;39] years, p<0.001). In patients with HTN we observed higher prevalence of DM (25.5% vs 1.4%, p<0.001), LVH (37.0% vs 1.5%, p<0.001) and proteinuria (52.0% vs 37.8%, p=0.037), than in those without HTN. Hypertensive patients were more obese (28.1 [25.0;31.9] vs 22.1 [20.2;24.8] kg/m^2, p<0.001), showed higher values of ePWV (9.2 [7.4;10.7] vs 6.2 [5.8;6.7] m/s, p<0.001) and ESR (12 [6;25] vs 7 [4;19] mm/hour, p=0.02), but lower GFR (67.1 [47.6;90.0] vs 103.9 [80.5;118.1] ml/min, p<0.001).

There was a steady decline in proportion of low risk patients and rise of prevalence of high risk patients with rise of grade of HTN (Fig. 1). Low-to-moderate risk patients showed higher proportion of low risk patients of CKD progression, than high-to-very-high risk patients.
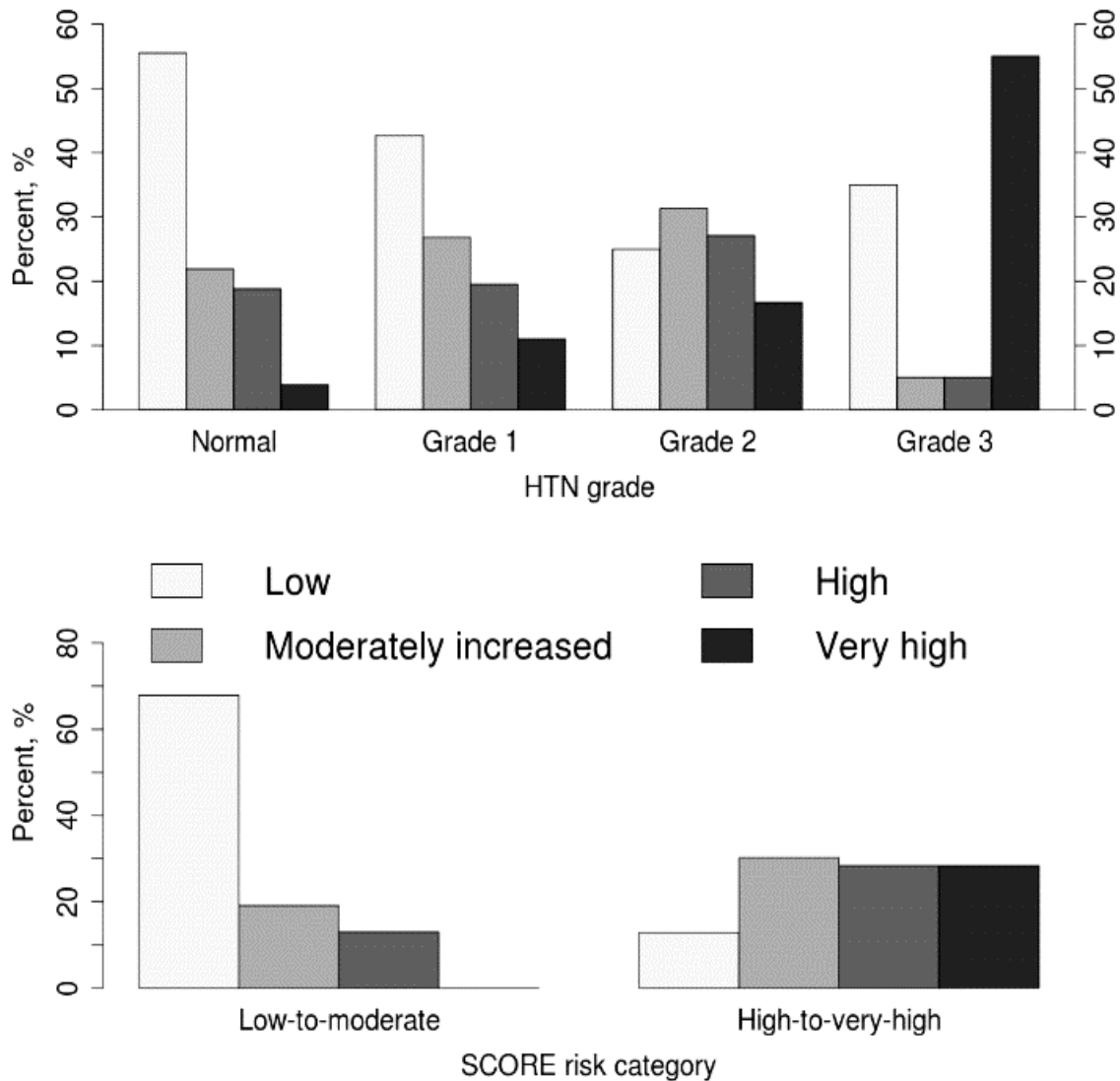
Notes. HTN, arterial hypertension.

Fig. 1. Distribution of risk of CKD progression in patients subdivided by grade of HTN and cardiovascular risk

The majority of normotensive patients were related to low-risk patients – 55.5% (Fig. 1). While the greatest proportion of patients with HTN also had low risk of CKD progression (Table 1), they were markedly more prevalent among high-risk patients.
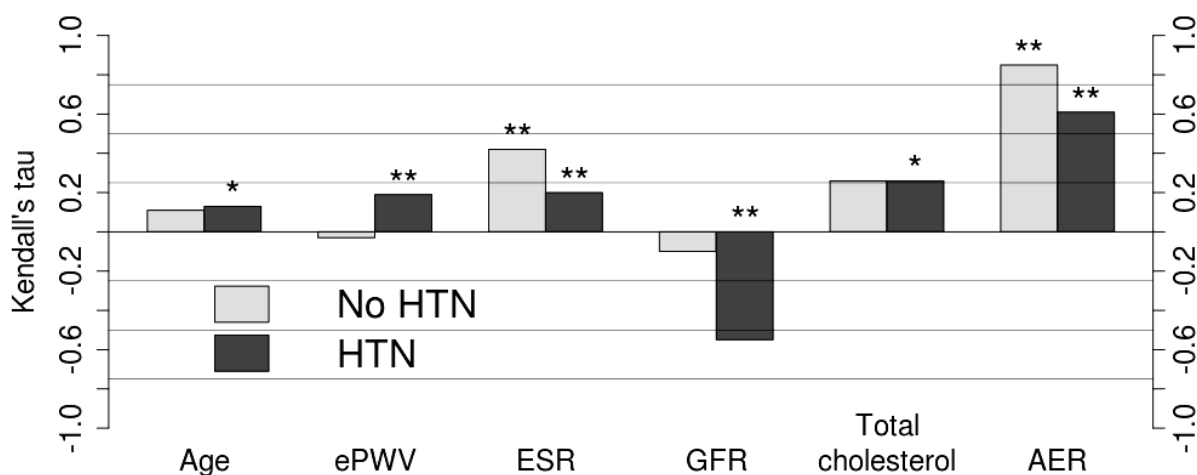
In patients with HTN risk of CKD progression was significantly associated with age, ePWV, ESR, total cholesterol, GFR and AER, while in patients without HTN it was connected only to ESR and AER (Fig. 2).

Our findings support strong interconnection of HTN and risk of CKD progression. Increase of nephrological risk was accompanied by deterioration of the majority of laboratory and instrumental parameters and rise of comorbidities (Table 1). This trend was more expressed in patients with low and moderately increased risk of CKD progression, that may be explained by younger age of low-risk patients. Despite age parity of patients with moderately increased, high and very-high risk of CKD progression (p=0.61), there were steady rises of systolic BP, diastolic BP and ePWV. Control of HTN in patients under our study was poor (<35%), being the worst for patients with high risk of CKD

progression and ePWV is the novel CV disease risk factor, calculated from age and mean BP [6, 10]. It correlated significantly (p<0.001) with age (ρ=0.84), SBP (ρ=0.65), DBP (ρ=0.56) and may be considered for assessment both cardiovascular and nephrological prognosis. Elevation of ESR may reflect increase of inflammatory activity, that, in turn, may

influence the course of atherosclerosis [12]. Notably, that this association was stronger for normotensive patiens (Fig. 2). Lack of statistical significance in models with total cholesterol may be the sequence of high percentage of missing data. Interestingly, that risk of CKD progression was poorly associated with duration of CKD but was related to duration of HTN.

Notes: HTN, arterial hypertension; ePWV, estimated pulse wave velocity; ESR, erythrocyte sedimentation rate; AER, albumin excretion rate; * - p<0.05; ** - p<0.001.

Fig. 2. Correlation analysis of patients' characteristics and risk of CKD progression in patients subdivided by presence of HTN

Hypertensive patients had unfavourable clinical and laboratory characteristics, as compared to normotensive ones. Uncontrolled HTN leads to deterioration of both renal and cardiovascular outcomes, and in our study it significantly affected both cardiovascular and nephrological risk profiles. Results of this section may be confounded by substantial difference in age and DM prevalence between groups. But this fact adds importance to DM and HTN as powerful risk factors of loss of renal function [3]. On the Figure 1 it is shown that the main contributors to high-risk groups of CKD progression were patients with HTN as well as patients with high-to-very-high risk of cardiovascular complications. After the correlation analysis (Figure 2) we found that in hypertensive patients risk of CKD progression was connected with both cardiovascular and nephrological risk factors, while in patients without HTN it was related only to nephrological ones (mainly to AER).

There is the evidence that one time urine estimation is non-inferior to daily urine protein excretion assessment [5, 18]. Only 66% of patients with elevated risk of CKD progression and 78% of

patients with AER>30 mg/24 hours had protein loss in first urine void. Thus, assessment of proteinuria in morning void may lead to underestimation of risk of CKD progression. Moreover, only 52% of patients with HTN had proteinuria and there was no difference in AER between patients with and without HTN.

In the meta-analysis of Mahmoodi et al. (2012) risk of the end stage renal disease was associated with GFR and urine albuminuria and was not influenced by HTN status [2]. HTN is a major cause of end stage renal disease and there is poor association between HTN in CKD and urine protein loss [3] – this thesis was confirmed in our study. Risk underestimation in usage of conventional charts is a common problem in nephrology [7] and cardiology [8], that may be explained by regional differences of the populations [7]. Correction of proteinuria and GFR has proven beneficial impact on prognosis [1, 21], but these treatment targets are difficult to reach. HTN is a powerful factor of prognosis, that is relatively simply corrected. Although HTN does not influence risk estimation [2], it affects outcomes [3], and, thus, should be incorporated to assessment of risk of CKD progression.

CONCLUSIONS

1. Increase in risk of CKD progression is associated with rise of burden of cardiovascular risk factors.

2. HTN and BP values should be accounted in assessment of risk of CKD progression.

Limitations.

1. Significant age difference between patients with and without HTN impedes extrapolation of our results on the whole population of CKD patients.

2. Patients in our study needed nephrologist's consultation due to appearance of new symptoms or deterioration of CKD, and, thus, are not completely representative for patients with CKD in ambulatory practice.

Conflict of interest: the authors declare no conflict of interest.

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