Prevalence of incidental chronic kidney disease and patient characteristics - results of the EH-UH 2 study and the ENAH project

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Abstract:

Introduction: Chronic kidney disease (CKD) is an independent risk factor for cardiovascular (CV) disease and premature deaths. The worldwide prevalence of CKD in 2017 in the general population is 9.1%. In this paper our primary aim was to present preliminary data on incidental, i.e., newly discovered CKD and the overall prevalence of CKD in the adult population in Croatia. Secondary aim was to compare these data with the data of the CKD prevalence of the adult population from the rural part of Croatia (results of the ENAH study).

Materials and Methods: This cross-sectional observational study included random, representative sample of general adults in Croatia, 781 subjects who were part of the large cohort from the EH-UH 2 study. The eGFR was calculated by creatinine-based CKD EPI equation. Albuminuria was determined from the albumin to creatinine ratio in urine (ACR) in 691 subjects.

Results: The overall prevalence of CKD in Croatia was 12.7%, of which 9.5% were newly discovered CKD, and only 3.2% were subjects with previously known CKD. According to the albuminuria level, 30.7% of the adult population belonged to the group with a moderate risk of CKD progression, and 7% had a high risk, while 2.5% of the study subjects had a very high risk. Predictors for newly discovered CKD are older age, higher urate and potassium, antihypertensive therapy, angina pectoris, atrial fibrillation, lower hemoglobin level.

Conclusions: These results continue in a pilot project of the Croatian Kidney Society and the Croatian Hypertension League on the implementation of an action plan to detect new kidney disease in the general population in real life, in a collaboration of primary care physicians and nephrologists.

Keywords: Chronic Kidney Disease, CKD EPI equation, albuminuria, estimated glomerular filtration rate, EH-UH 2

Sažetak:

Prevalencija incidentne kronične bubrežne bolesti i karakteristike ispitanika - rezultati EH-UH 2 i ENAH studija

Uvod: Kronična bubrežna bolest (KBB) nezavisni je čimbenik rizika za kardiovaskularne (KV) bolesti i preranu smrt. Svjetska prevalencija KBB u 2017. godini u općoj populaciji iznosi 9,1%. U ovom

radu primarni nam je cilj bio prikazati preliminarne podatke o incidentnoj, odnosno novootkrivenoj KBB i ukupnoj prevalenciji KBB u odrasloj populaciji u Hrvatskoj. Sekundarni cilj bio je usporediti ove podatke s podacima o prevalenciji KBB odrasle populacije u ruralnom dijelu Hrvatske (rezultati ENAH studije).
Materijali i metode: Ova opservacijska presječna studija uključivala je slučajni, reprezentativni uzorak opće odrasle populacije u Hrvatskoj, 781 ispitanika koji su bili dio EH-UH 2 studije. eGFR je izračunat pomoću CKD EPI jednadžbe, albuminurija je određena na temelju omjera albumina i kreatinina u urinu (ACR) u 691 ispitanika.
Rezultati: Ukupna prevalencija KBB u Hrvatskoj iznosi 12,7%, od čega je 9,5% novootkrivena KBB, a samo 3,2% ispitanika od ranije zna za KBB. Prema razini albuminurije 30,7% odrasle populacije pripadalo je skupini s umjerenim rizikom od napredovanja KBB, a 7% je imalo visok rizik, dok je 2,5% ispitanika imalo vrlo visok rizik. Prediktori za novootkrivenu KBB su starija dob, više vrijednosti urata i kalija, antihipertenzivna terapija, angina pectoris, fibrilacija atrija, niža razina hemoglobina.
Zaključak: Ovi rezultati nastavljaju se u pilot projekt Hrvatskoga društva za bubreg i Hrvatske lige za hipertenziju o provođenju akcijskog plana za otkrivanje novonastale bubrežne bolesti u općoj populaciji u stvarnom životu, suradnjom liječnika obiteljske medicine i nefrologa.

Ključne riječi: Kronična bubrežna bolest, CKD EPI jednadžba, albuminurija, procijenjena brzina glomerularne filtracije, EH-UH 2

Introduction

Chronic kidney disease (CKD) is an independent risk factor for cardiovascular (CV) disease and premature deaths (1,2,3). It has become a major global health, economic and financial burden with more than 2-3% of annual health-care budget spend in high-income countries on the management of the CKD (4,5). According to the Global Burden of Disease Study, in 2017 around 1.2 million deaths worldwide were caused by CKD and that number is projected to rise to 2.2 million at best to as much as 4 million at worst by the year 2040 (5). As the leading cause of death in the period from year 1990 to 2017, CKD came from 17th to 12th place, and it is predicted that by the year of 2040 it will be in 5th place (5). There is a significant difference in global prevalence among the genders, with a higher prevalence of CKD in women (11.8%) than men (10.4%), but men have shown to progress more rapidly to end-stage renal disease (ESRD) (5). According to the results of the latest epidemiological studies, the worldwide prevalence of CKD in 2017 in the general population is 9.1%, with an observed increase trend of 29.3% in the period of year 1990 to 2017 (5). This major increase in prevalence over time is explained by the increase in the prevalence of the most important risk factors leading to the development of CKD, and they are: arterial hypertension, diabetes, and obesity (1,2,5). CKD is associated not only with the risk of ESRD and the need for replacement therapy but is already an independent CV risk factor in the early stages. Studies have shown that only one in five patients with CKD experience the need for replacement therapy, while the rest die most often from CV or cerebrovascular deaths (6,7,8). A significant increase in the incidence of ESRD requiring haemodialysis and kidney transplant replacement therapy was observed (43.1% and 34.4%, respectively) between year 1990 and 2017 (5). Data on the prevalence of the CKD in the general population in Croatia have been insufficient, due to that, one of the goals of Epidemiology of arterial hypertension and salt intake in Croatia - The Croatian Science Foundation (EH-UH 2) study (IP-06-2016) is to determine the prevalence of CKD in Croatia (to determine the CKD stage according to the estimated glomerular filtration rate (eGFR) and albuminuria). In this paper our primary aim was to present preliminary data on incidental, i.e., newly discovered CKD and the overall prevalence of CKD in the adult population in Croatia. Secondary aim was to compare these data with the data of the CKD prevalence of the adult population from the rural part of Croatia (results of the ENAH study - Endemic Nephropathy in Croatia-epidemiology, diagnosis and etiopathogenesis study), and to compare these data with world data on CKD prevalence.

Materials and methods

Patient data and methods

This cross-sectional observational study included random, representative sample of general adults in Croatia, 781 subjects who were part of the large cohort from the EH-UH 2 study. Subjects were invited to participate and were examined on a door-to-door basis. Exclusion criteria were age under 18 age, terminal stage of

malignant disease, dementia, amputation, or immobilization of one limb, current acute illness, convalescence after operational intervention and unsigned consent.
Physicians and trained nurses collected the data through epidemiological questionnaires, medical history, and clinical examination. All study personnel were trained to collect survey and clinical information in a standardized manner. Participants completed an extensive questionnaire, provided a spot urine, fasting blood sample and 24-hour urine. Weight and height were measured, and the body mass index (BMI) was calculated. Abdominal obesity was defined as waist circumference for males > 102 cm and for females > 88 cm. Blood pressure (BP) was measured three times on the non-dominant arm by an Omron M6 device as per ESH/ECS guidelines. Hypertension was defined as BP ≥140/90 mmHg and/or the use of antihypertensive drugs. Diabetes was defined as fasting blood glucose >7 mmol/L and/or the use of antidiabetic drugs. CKD was defined as an eGFR <60 mL/min/1.73 m^2; CKD stages were classified according to the Kidney Disease Improving Global Outcomes guidelines into 5 stages. The eGFR was calculated by creatinine-based CKD EPI equation. Albuminuria was determined from the albumin to creatinine ratio in urine (ACR) in 691 subjects in whom we had a complete urine analysis finding. The CKD EPI equation is shown below:

	Race and gender	Serum creatinine μmol/L (mg/dl)	Equation (ml/min/1.73 m^2)
CKD-EPI	Caucasian women	≤62 (≤0.7)	$eGFR = 144 \times (Scr/0.7)^{-0.329} \times (0.993)^{Age}$
		>62 (>0.7)	$eGFR = 144 \times (Scr/0.7)^{-1.209} \times (0.993)^{Age}$
	Caucasian men	≤80 (≤0.9)	$eGFR = 141 \times (Scr/0.9)^{-0.411} \times (0.993)^{Age}$
		>80 (>0.9)	$eGFR = 141 \times (Scr/0.9)^{-1.209} \times (0.993)^{Age}$

Statistical analysis

Categorical variables were shown as percentages and continuous variables as means with standard deviation for normally distributed variables or medians with interquartile range (25th and 75th percentiles) for non-normally distributed. Categorical variables were compared using chi-square or Fischer exact test. Continuous variables were compared using independent sample t-test, paired-samples t-test, or Mann-Whitney U-test, depending on the distribution. Statistical significance was set, and statistical analysis was performed at 0.05 using SPSS version 23.0 (IBM Corp., USA).

Results

PREVALENCE OD CKD ACCORDING TO THE CKD STAGE AND ALBUMINURIA – EH-UH 2 AND ENAH STUDY

The overall prevalence of CKD in Croatia was 12.7%, of which 9.5% were newly discovered CKD, and only 3.2% were subjects with previously known CKD. Our results are in line with result from other studies. According to the latest data from the National Health and Nutrition Survey, the prevalence of CKD in the U.S. is just under 15%, with a significantly higher increase in the prevalence of CKD in old population, i.e., subject older than 65 years (38.1%) (9). There was a higher prevalence in women than men in the U.S. (14.3% vs. 12.4%) (9). Interestingly, even in the U.S. as many as 9 in 10 adults do not know they have CKD, and as many as 2 in 5 adults do not know they have advanced stage of CKD (10). In other large epidemiological studies, the prevalence of CKD was between 7.2% -13% (5,11).
The prevalence of CKD in rural areas (results from the ENAH study) was slightly lower than in general population of Croatia (8.8%), but with a significant increase in the prevalence of CKD in subject older than 65 years, when it went up to 29.44% (12). There was also a trend of higher prevalence in women compared to men (9.9% vs. 7.2%) (12).
In our study when we considered not only eGFR category but also albuminuria and according to that, 30.7% of the adult population belonged to the group with a moderate risk of CKD progression, and 7% had a high risk, while 2.5% of the study subjects had a very high risk, Figure 1. One of the most important predictors of risk of CKD progression leading to renal failure, dialysis, increased CV risk, and premature mortality is elevated albuminuria. Through the division according to eGFR category and albuminuria status, patient risk can be more ac-

curately defined as low, moderately increased, high, or very high risk of renal impairment and other complications, thus facilitating decision-making on patient monitoring and management. It should be also noted that patients without reduced eGFR, but with increased albuminuria are at higher risk of CV and renal incidents. Therefore, considering albuminuria has a significant advantage for early detection of such patients, proactive treatment of their disease and planning health resources. Our results are consistent with the results from systematic review by Morton et al. who reported that the overall prevalence of CKD (stages G3–5) was 2–17% when they considered seven studies from the USA, China, and Italy (13). The prevalence was lower in China (2–3%) and Italy (3%) than in the U.S. (6–17%) (13). In individual studies (stages G2–5): the prevalence according to the stages of albuminuria was A1: 27.4–56.4%, A2: 2.9–10.0%, A3: 0.4-3.2% (13). This systematic review of epidemiological studies on the prevalence of CKD also considered eGFR category and albuminuria status. This provides a very valuable different perspective from previous studies that classified the prevalence of CKD according to only the eGFR stage and thus does not identify patients or subjects at greatest risk of fatal and nonfatal outcomes and further progression of renal function. Our results from the EH-UH 2 study reveal that a significant portion of the general population in Croatia has CKD and is at moderate risk for progression of renal function, which is important in early detection of these patients and planning their further health care and risk reduction and improving quality of life and survival.

CHARACTERISTIC OF THE STUDY POPULATION – EH-UH 2

The characteristics of the study population are shown in Table 1. Study included 682 subjects with normal kidney function (eGFR CKD EPI ≥60 mL/min/1.73 m^2), 74 subjects with newly discovered CKD, and 25 subjects with CKD that was known before. The oldest subjects were those with newly discovered CKD, age 74.5 (67-80), and the youngest subjects with normal renal function, age 57.0 (46-66), p<0.001. Both subjects with newly discovered CKD and previously known were obese, body mass index (BMI) 30.17±4.79; 30.91±6.67, p=0.549. Body surface area (BSA) value of our population differs significantly than the recommended BSA value of 1.73 m^2, to which most creatinine eGFR equations are adjusted. Our BSA values were for normal renal function, newly discovered CKD, and previously known CKD, 1.93±0.24; 1.88±0.31; 2.02±0.25, p=0.058, respectively. Even 32.0% of subjects with previously known CKD were smokers. Uric acid and serum creatinine values were highest in the group with newly discovered CKD, while albuminuria was highest in the group with previously known CKD. The highest prevalence of diabetes and arterial hypertension was in the group with newly discovered CKD, while the highest prevalence of myocardial infarction, angina pectoris and cerebrovascular stroke was in the group with previously known CKD, Table 2. Many CKD patients had a positive family history of arterial hypertension or one of the earlier mentioned diseases. In the group with newly discovered CKD, as many as 50% of subjects said that their parents suffered from arterial hypertension, and in about 12% one of the parents died of sudden death before the age of 55, Table 1.

We often ask ourselves what are the characteristics of a patient with undetected CKD who comes to the primary care office for examination. Our results show that it is the patient who most often suffers from arterial hypertension and / or diabetes, who is overweight, older, and more often female. Those are also the risk factors that Centers for Disease Control and Prevention state as the most important risk factors that we need to act on in better control and prevention of CKD (10).

Our results showed that the prevalence of CKD increases with older age. In our research group, the prevalence of CKD is growing rapidly between the 6th and 7th decades. These results are similar to the results of the ENAH study were there is also an increase of CKD prevalence between the 6th and 7th decades, in men 2.0% to 15.0% and in women 3.3% to 14.6%. Similar results are presented in a systematic analysis by Mills et al. but a decade earlier, in men 3.0% to 9.7% and in women 4.0% to 13.1% (2).

Results from multinomial logistic regression are showed in Table 3. Subjects with higher values of uric acid, potassium, older age, and angina pectoris were more likely to have newly discovered CKD than subjects with previously known CKD. Also, antihypertensive therapy and higher body height were negative predictors of previously known CKD compared to newly diagnosed CKD. On the other hand, hemoglobin and atrial fibrillation were negative predictors of normal renal function compared to the newly discovered CKD. Subjects with higher values of uric acid, potassium, and the elderly were more likely to have newly discovered CKD than subjects with normal renal function.

Discussion

ACTION PLAN TO DETECT NEW KIDNEY DISEASE

Our results are consistent with data from other studies. The prevalence of CKD in Croatia is 12.7% with a high percentage of newly discovered CKD. The prevalence of CKD is high in the general and rural population, with a higher prevalence among women. Predictors for newly discovered CKD are older age, higher urate and potassium, antihypertensive therapy, angina pectoris, atrial fibrillation, lower hemoglobin level.

The limitation of our study is that eGFR and albuminuria values were determined only once and we have no follow-up data after 3 months, but this is the case with most large epidemiological studies. The advantages of this study are that a large number of subjects are involved, and these are the first such data in Croatia. The results of EH-UH 2 indicate the need for a national pro-

gram for early detection of CKD. The CKD should be a central part of future public health planning and patients at risk of CKD should receive special care in primary care practices. Diabetes and high blood pressure are the more common causes of CKD in adults and managing blood sugar and blood pressure can help keep kidneys healthy.

These results continue in a pilot project of the Croatian Kidney Society and the Croatian Hypertension League on the implementation of an action plan to detect new kidney disease in the general population in real life, in a collaboration of primary care physicians and nephrologists.

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The authors have no conflicts of interest to declare.

Table 1. Demographic and clinical characteristics of study population

	Normal kidney function N=682	Newly discovered CKD N=74	CKD known before N=25	P value
Gender, % (N) - Men - Women	 34.5 (235) 65.5 (447)	 32.4 (24) 67.6 (50)	 48.0 (12) 52.0 (13)	0.247
Age, year	57.0 (46.0-66.0)	74.5 (67-80)	63.0 (55-70)	<0.001
BMI, kg/m^2	28.95 ± 5.60	30.17 ± 4.79	30.91 ± 6.67	0.549
BMI category, % (N) - <25 kg/m^2 - 25-30 kg/m^2 - >=30 kg/m^2	 27.9 (190) 34.6 (236) 37.5 (256)	 13.9 (10) 38.9 (28) 47.2 (34)	 12.0 (3) 40.0 (10) 48.0 (12)	0.972
BSA Mosteller, m^2	1.93 ± 0.24	1.88 ± 0.31	2.02 ± 0.25	0.058
Systolic blood pressure, mmHg	133.66 ± 17.65	140.05 ± 24.57	143.15 ± 20.85	0.574
Diastolic blood pressure mmHg	83.13 ± 9.86	80.69 ± 12.86	82.35 ± 10.05	0.559
Smoking status, % (N) - Never - Ex - Current smoker	 56.2 (383) 17.0 (116) 26.8 (183)	 73.0 (54) 18.9 (14) 8.1 (6)	 40.0 (10) 28.0 (7) 32.0 (8)	0.003
Haemoglobin, g/L	141.0 (133.0-151.0)	137.00 (126.0-147.0)	145.00 (130.8-157.3)	0.065
Glucose, mmol/L	4.70 (4.3-5.3)	5.40 (4.9-6.7)	5.30 (4.6-6.2)	0.560
Urate, umol/L	277.0 (231.0-336.3)	361.5 (310.0-421.0)	290.0 (269.3-370.0)	0.012
Cholesterol, mmol/L	5.20 (4.5-6.0)	4.80 (4.1-5.6)	5.0 (3.9-6.1)	0.899
Triglyceride, mmol/L	1.21 (0.9-1.7)	1.57 (1.0-2.1)	1.34 (0.97-1.68)	0.641
HDL-cholesterol, mmol/L	1.41 (1.2-1.7)	1.41 (1.1-1.6)	1.25 (1.13-1.77)	0.742
LDL-cholesterol, mmol/L	3.11 (2.4-3.9)	2.55 (2.0-3.3)	2.65 (1.88-3.83)	0.711
Potassium, mmol/L	4.50 (4.3-4.8)	4.70 (4.3-5.0)	4.40 (4.1-4.9)	0.082
Sodium, mmol/L	141.00 (140.0-143.0)	141.50 (140.0-143.0)	141.0 (140.0-142.0)	0.689
Calcium - total, mmol/L	2.37 (2.3-2.4)	2.38 (2.3-2.5)	2.40 (2.23-2.43)	0.169
Phosphates, mmol/L	1.06 (0.9-1.2)	1.06 (0.9-1.1)	1.08 (0.99-1.16)	0.573
Creatinine, umol/L	69.0 (62.0-80.0)	103.50 (89.0-118.0)	82.0 (63.7-99.3)	0.011
ACR, mg/g	17.35 (7.54-38.99)	30.57 (13.2-80.8)	49.76 (13.5-94.1)	0.021
Arterial hypertension, % (N) - Mother - Father	 52.5 (358) 36.1 (246)	 39.2 (29) 16.2 (12)	 40.0 (10) 24.0 (6)	 0.191 0.070
Death of a parent before the age of 55, % (N) - Mother - Father	 4.4 (30) 4.4 (30)	 8.1 (6) 4.1 (3)	 16.0 (4) 12.0 (3)	 0.014 0.049

BMI – body mass index, BSA – body surface area, ACR – urine albumin to creatinine ratio

Table 2. Prevalence of diseases

	Normal kidney function N=682	Newly discovered CKD N=74	CKD known before N=25	P value
Arterial hypertension, % (N)	49.9 (338)	89.2 (66)	80.0 (20)	0.309
Angina pectoris, % (N)	3.7 (25)	9.5 (7)	24.0 (6)	0.149
CVI ischemic, % (N)	2.1 (14)	5.4 (4)	12.0 (3)	0.520
CVI haemorrhagic, % (N)	0.4 (3)	1.4 (1)	4.0 (1)	0.987
TIA, % (N)	1.5 (10)	6.8 (5)	4.0 (1)	0.976
Atrial fibrillation, % (N)	2.2 (15)	13.5 (10)	12.0 (3)	0.900
Myocardial infarction, % (N)	1.9 (13)	2.7 (2)	12.0 (3)	0.197
Heart failure, % (N)	0.6 (4)	4.1 (3)	8.0 (2)	0.813
Diabetes, % (N)	11.2 (76)	33.8 (25)	32.0 (8)	0.968

CVI - cerebrovascular insult, TIA - transient ischemic attack

Table 3. Multinomial logistic regression

Reference category - newly discovered CKD		OR	95% CI	P value
Known CKD	Uric acid, umol/L	0.988	0.98-0.99	0.002
	Potassium, mmol/L	0.242	0.06-0.91	0.036
	Age, year	0.093	0.87-0.98	0.011
	Height, cm	1.087	1.02-1.17	0.017
	Angina pectoris	0.126	0.02-0.83	0.031
	Antihypertensive therapy	6.613	1.25-34.99	0.026
Normal kidney function	Hemoglobin, g/L	1.031	1.01-1.06	0.034
	Uric acid, umol/L	0.985	0.98-0.99	<0.001
	Potassium, mmol/L	0.453	0.21-0.97	0.042
	Age, year	0.905	0.87-0.94	<0.001
	Atrial fibrillation	4.072	1.56-14.30	0.028

EH-UH 2 N=691	A1 ACR <30 mg/g % (N)	A2 ACR 30-300 mg/g % (N)	A3 ACR >300 mg/g % (N)
G1	33.6 (232)	13.5 (93)	1.4 (10)
G2	26.0 (180)	13.3 (92)	1.6 (11)
G3a	3.9 (27)	3.3 (23)	0.9 (6)
G3b	0.7 (5)	0.7 (5)	0.1 (1)
G4	0	0.1 (1)	0.6 (4)
G5	0	0.1 (1)	0

Figure 1. Prognosis of CKD by GFR and albuminuria categories.

Green, low risk of disease progression; yellow, moderately increased risk of disease progression; orange, high risk of disease progression; red, very high risk of disease progression. CKD chronic kidney disease, GFR - glomerular filtration rate, ACR - albumin-to-creatinine ratio

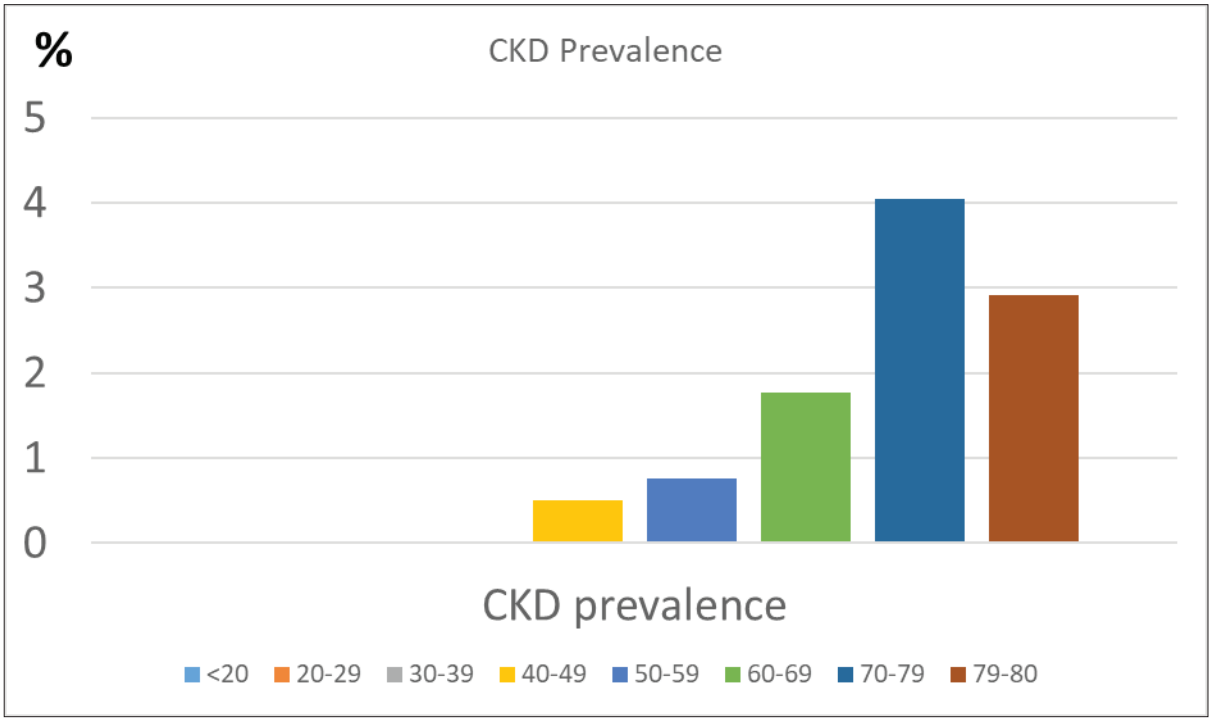

Figure 2. CKD prevalence according to decades

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