 Prague Medical Report / Vol. 124 (2023) No. 3, p. 242–254

The Predictive Value of Serum Aldosterone Level for Coronary Artery Calcium Score in Patients with Chronic Kidney Disease: A Single-center Study

Viktor V. Semenov[1], Jizzo R. Bosdriesz[2], Olexandr Kuryata[1]
[1]Department of Internal Medicine 2 and Phthisiology, Dnipro State Medical University, Dnipro, Ukraine;
[2]ERA-EDTA Registry, Department of Medical Informatics, Amsterdam UMC, University of Amsterdam, Amsterdam Public Health Research Institute, Amsterdam, The Netherlands

Received September 21, 2022; Accepted August 27, 2023.

Key words: Aldosterone – Chronic kidney disease – Coronary artery calcium score – Prediction

Abstract: Patients with chronic kidney disease (CKD) have high cardiovascular risk (CVR), which is often underestimated by conventional tools. The coronary artery calcium score (CACS) significantly improves CVR stratification by conventional tools, but it is often not available in low-resources settings. Aldosterone may be a cheaper alternative to CACS for CVR assessment in CKD patients. The aim was to assess the ability of serum aldosterone level to predict CACS in patients with CKD in comparison to standard predictors. This single-center study included 57 patients aged 40 to 67 years with CKD (estimated glomerular filtration rate [eGFR] ≥45 ml/min) and arterial hypertension. Serum aldosterone, sex, age, body mass index, blood pressure, total cholesterol, eGFR, and proteinuria were used for prediction of CACS>0 Agatston units (AU) and CACS>100 AU. The area under the curve (AUC) with 95% confidence intervals (CI) and the mean Brier scores were examined for predictors of CACS. Aldosterone predicted a CACS>100 AU

This study was supported from European Renal Association – European Dialysis and Transplantation Association during ERA-EDTA Registry Fellowship at the Department of Medical Informatics, Amsterdam UMC, University of Amsterdam. The reagent for measurement of serum aldosterone was purchased with the support from Dnipro State Medical University, Dnipro, Ukraine.

Mailing Address: Viktor V. Semenov, PhD., Dnipro State Medical University, Vernadskoho Street 9, Dnipro, 49000, Ukraine; Phone: +380 984 334 841; e-mail: semenovviktvikt@gmail.com

https://doi.org/10.14712/23362936.2023.19

(AUC = 0.72, 95% CI: 0.56–0.88), but not a CACS>0 AU. Age predicted a CACS>100 AU (AUC = 0.80, 95% CI: 0.67–0.93) and a CACS>0 AU (AUC = 0.75, 95% CI: 0.62–0.89). The addition of aldosterone to age for prediction of a CACS>100 AU improved the mean Brier score, compared to the model with age alone, from 0.16 to 0.14, but not the AUC (0.83, 95% CI: 0.70–0.95). Aldosterone was a significant predictor of a CACS>100 AU in patients with CKD, but aldosterone was not a better predictor than age alone.

Introduction

Patients with chronic kidney disease (CKD) are known to have increased overall and cardiovascular mortality (Matsushita et al., 2016), mostly due to a higher risk of atherosclerosis development (Valdivielso et al., 2019). Cardiovascular risk stratification is usually done with simple and reliable tools, such as the SCORE and Framingham risk chart (D'Agostino et al., 2008; Piepoli et al., 2016). These tools work well in the general population, but underestimate risk in individuals with CKD (Matsushita et al., 2016). Accounting for additional markers may improve the predictive ability of standard tools. The most powerful improvement of cardiovascular risk prediction made by standard tools was shown by coronary artery calcium score (CACS) (Osawa et al., 2016; De Lemos et al., 2017), which works well both for the general population and for patients with CKD (Chen et al., 2017). CACS is based on computed tomography scanning of the heart with the measurement of the calcium in the coronary arteries. It is a simple and reliable test for risk reassessment which does not require special preparation of the patient (Zhao et al., 2014). However, its implementation in low-income countries may be problematic. For instance, in Ukraine, the healthcare system provides approximately 25 $ for the yearly follow-up of a middle-aged person in primary care (Orange Health Consultants, 2018), while the lowest estimated cost for the use of CACS is 85 $ (Van Kempen et al., 2011). Feasibility is a crucial factor of tests for early diagnosis of cardiovascular disease. Moreover, in low- and middle-income regions (including Eastern Europe), only modest reductions in coronary artery disease related mortality have been observed in the last decades, which may be related to the lower investments in their healthcare systems (Moran et al., 2014).

For individuals with limited access to CACS, aldosterone may be a candidate biomarker for the identification of persons with poor cardiovascular prognosis. CKD itself predisposes to excessive production of aldosterone (Hayashi et al., 2018). In addition, up to 86% of patients with CKD have arterial hypertension (HTN) (Judd and Calhoun, 2015), for which the first-line drugs are angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) (Whelton et al., 2018; Williams et al., 2018). Their usage may result in a higher production of aldosterone, which is also called aldosterone "breakthrough" (Schrier, 2010). Aldosterone is the main driver of the renin-angiotensin-aldosterone (RAAS) system,

which has pleiotropic effects on the cardiovascular system (rising of systemic blood pressure [BP], cardiac fibrosis, pro-inflammatory activity, vascular calcification) and kidneys (renal fibrosis, CKD progression) (Donderski et al., 2017). Measuring the aldosterone level is much simpler and more feasible than the investigation of coronary calcium, and therefore may be implemented in routine clinical practice in the settings of limited access to CACS measurement.

To date, no study assessed the potential prognostic value of aldosterone for cardiovascular events in patients with CKD. The ability of aldosterone to predict cardiovascular mortality or hospitalization was not yet assessed in patient with CKD, but in two previously performed prognostic studies in patients with heart failure it was assessed, with inconsistent results (Güder et al., 2007; Kobayashi et al., 2020). Therefore, the aim of this study was to assess the ability of serum aldosterone level to predict CACS in patients with CKD.

Methods

Study population

Patients for this study were enrolled from January 2018 till July 2019 at the Dnipropetrovsk Mechnikov Regional Hospital, Dnipro, Ukraine. Inclusion criteria were: age between 40 and 70 years, established diagnosis of CKD stages 1–3a (estimated glomerular filtration rate [eGFR] ≥ 45 ml/min), grades I–II HTN (systolic BP < 180 mm Hg, diastolic BP < 110 mm Hg), and treatment with ACEi/ARB in combination with other first-line antihypertensive drug for at least 3 months prior to the enrolment to the study. None of the patients were treated with aldosterone receptor blockers at the moment of data collection. 33 of 57 patients (57.9%) were receiving treatment with statins at the moment of data collection. Exclusion criteria were: the presence of cardiovascular disease, nephrotic syndrome (urine protein loss > 3.5 g/24 hours), severe deviations of serum potassium level (<3 of >6 mmol/l), type 1 diabetes mellitus (DM), type 2 DM requiring insulin therapy, arrhythmia that required pharmacological treatment, thyroid gland function abnormalities, and presence of malignancies or hereditary anomalies of the urinary tract.

Diagnosis of CKD was based on KDIGO Guidelines for Evaluation and Management of CKD (Eknoyan et al., 2013). Patients in the study who fulfilled the diagnosis of CKD had abnormalities of kidney function or structure for more than 3 months (eGFR < 60 ml/min, or albuminuria > 30 mg/24 hours, or urine sediment abnormalities, or structural kidney abnormalities detected by kidney ultrasound) (Eknoyan et al., 2013). Diagnosis of HTN was established according to ESC Guidelines for the Management of Arterial Hypertension (Mancia et al., 2013; Williams et al., 2018). Patients were recommended to restrict salt intake to less than 5 g per day for at least 3 months prior to the enrolment to the study (Eknoyan et al., 2013).

Compliance with ethical standards
All the patients gave their written informed consent to the collection and processing of the data. The study was approved by the Ethical Committee of Dnipropetrovsk Mechnikov Regional Hospital, Dnipro, Ukraine.

Measurements
CACS
CACS was obtained using computed tomography coronarography, and computed tomography scans were performed using Optima CT660 (GE Healthcare, Wisconsin, USA). CACS was reported in Agatston units (AU). The decision to classify CACS as negative (0 AU), moderate (1–100 AU) or high (>100 AU) was based on the 2019 ESC/EAS Guidelines for the management of dyslipidaemias (Mach et al., 2020) and on the study of Chen et al. (2017).

Aldosterone
Evaluation of the serum aldosterone level was performed using reagent Diagnostics Biochem Canada Aldosterone Elisa Kit, CAN-ALD-450. Blood for the analysis was taken after at least 8 hours of fasting and after the patient had been seated for 15 minutes. Blood samples were immediately centrifuged at room temperature at 2,000 rpm for 15 minutes. Serum was collected and stored at –20 °C. Serum aldosterone level was reported in pg/ml.

Other variables
The following variables were investigated: sex, age, smoking status, body mass index (BMI), systolic BP (SBP), diastolic BP (DBP), total cholesterol (TC), eGFR and the presence of proteinuria.

Age was reported in years. BMI was calculated as weight (kg)/height $(m)^2$. BP evaluation was performed using the automated method and reported in mm Hg. Assessment of blood TC, creatinine and urine protein presence were performed using standard methods. eGFR was calculated using the CKD-EPI equation, which requires patients' sex, ethnicity, age and serum creatinine, and reported in ml/min (Eknoyan et al., 2013). Proteinuria was defined as the presence of protein or protein trace in morning void.

Missing data
There were missing data for TC (13 patients, 22.8%) and eGFR (2 patients, 3.5%). Missing continuous values were omitted from the calculations.

Statistical analysis
Statistical analyses were performed using LibreOffice and R, version 3.6.3 (Sing et al., 2005; Robin et al., 2011; López-Ratón et al., 2014; Lele et al., 2019; Firke, 2020; R Core Team, 2020). The type of data distribution was assessed using a Shapiro-

Wilk test. In case of normal distribution, continuous data were presented as mean (with standard deviation) and groups were compared using one-way analysis of variance. In the case of non-normal distribution, continuous data were presented as median (with 25th and 75th percentiles) and groups were compared using the Kruskal-Wallis test. Categorical data were presented as n (%), and groups were compared using chi-square test.

The ability of variables in the study to predict a CACS > 0 AU and CACS > 100 AU was assessed. First, all variables available in clinical practice that are potentially associated with coronary calcification (i.e., sex, age, smoking status, BMI, SBP, DBP, TC, and eGFR), and serum aldosterone were included in univariate logistic regression models. Next, only significant predictors were included to the multivariate logistic regression model with addition of serum aldosterone (per 10 pg/ml) to assess its ability to improve the prediction. The assumption of linearity of eGFR with log odds of the outcome was violated and therefore the natural logarithm of eGFR was included in the logistic regression model. The mean Brier score was used to estimate the accuracy of the models (scores could range from 0 [perfect accuracy] to 0.25 [of no value]). To determine how well the model distinguished between individuals with and without the outcome, a receiver operating characteristic (ROC) curve was built with estimation of the area under the curve (AUC). Comparison of two AUCs was performed with the method by DeLong et al. (1988). For statistically significant predictors, optimal cut-off points were determined (i.e., values of the predictors that classify the highest number of study participants correctly) with the highest Youden's index (the sum of specificity and sensitivity). Calibration of the model was assessed with the Hosmer-Lemeshow goodness-of-fit test. The threshold for confirming statistical hypotheses was set at <0.05.

Results

The study included 57 patients of Caucasian ethnicity aged 40 to 67 years (Table 1). Mean eGFR of the patients in the study was 77.2 ml/min, and ranged from 45.3 ml/min to 108.3 ml/min. CKD stage 1 was diagnosed in 11 patients (19.3%), CKD stage 2 was diagnosed in 41 patients (71.9%), and CKD stage 3a was diagnosed in 5 patients (8.8%). 42 (73.7%) of the patients were females. Age and serum aldosterone differed significantly between patients with a CACS of 0 AU, 1–100 AU and >100 AU. Median serum aldosterone was the highest in patients with CACS > 100 AU, but there was no linear relation between aldosterone and CACS category. The proportion of females, smoking status, patients with diabetes mellitus and patients with proteinuria as well as the mean BMI, SBP, TC, eGFR and median DBP were not different between patients with CACS of 0 AU, 1–100 AU and >100 AU.

Using univariate logistic regression, age was the only significant predictor of CACS > 0 AU, whereas both age and aldosterone were significant predictors of CACS > 100 AU (Table 2). In the multivariate logistic regression model, both age and aldosterone significantly predicted CACS > 100 AU (Table 2).

Table 1 – Demographic, clinical and laboratory characteristics of CKD patients with CACS of 0 AU, 1–100 AU and > 100 AU

Variable	Total (n=57)	CACS			p-value
		0 AU (n=20)	1–100 AU (n=22)	> 100 AU (n=15)	
Age, years	56 (53; 59)	53 (49; 55)	55 (53; 59)	60 (57; 63)	<0.01
Females, n (%)	42 (73.7)	16 (80.0)	15 (68.2)	11 (73.3)	0.69
Smoking, n (%)	6 (10.5)	2 (10.0)	3 (13.6)	1 (6.7)	0.79
DM, n (%)	11 (19.3)	2 (10.0)	5 (22.7)	4 (26.7)	0.48
BMI, kg/m^2	31.9 (7.5)	29.6 (6.9)	33.5 (7.0)	32.5 (8.5)	0.21
SBP, mm Hg	139 (17.5)	138.5 (15.4)	137.4 (19.2)	142.2 (18.3)	0.58
DBP, mm Hg	85 (80; 95)	90 (80; 91.2)	85 (80; 96.5)	85 (80; 90.5)	0.99
TC, mmol/l	5.4 (1.1)	5.6 (1.3)	5.5 (1.2)	5.2 (1.0)	0.38
eGFR, ml/min	77.2 (13.4)	81.7 (12.8)	74.1 (14.4)	75.8 (12.0)	0.18
Proteinuria, n (%)	33 (57.9)	13 (65.0)	11 (50.0)	9 (60.0)	0.61
Serum aldosterone, pg/ml	31 (15; 51)	38 (18; 52)	18 (14; 34)	48 (30; 123)	0.01

CKD – chronic kidney disease; CACS – coronary artery calcium score; AU – Agatston units; DM – diabetes mellitus; BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure; TC – total cholesterol; eGFR – estimated glomerular filtration rate

The AUC for age was 0.75 (95% CI = 0.62–0.88) when predicting a CACS > 0 AU (Table 3). The AUC for age (0.80 [0.67–0.93]) was higher than that for aldosterone (0.72 [0.56–0.88]) when predicting CACS > 100 AU, but the difference of the AUCs was not significant (p=0.39) (Figure 1, Table 2). The addition of aldosterone on top of age in the prediction of CACS > 100 AU had led to a 10% improvement of the mean Brier score (from 0.16 to 0.14), but non-significant change in the AUC (0.83 [0.70–0.95]). The AUC of the model with age and aldosterone in the prediction of CACS > 100 AU was neither different from the AUC for the model with age alone (p=0.36), nor it was different from the model with aldosterone alone (p=0.16) (Figure 1, Table 2). According to our data the optimal cut-off point for age for the prediction of CACS > 0 AU was 57 years (sensitivity = 57%, specificity = 90%). For the prediction of CACS > 100 AU the optimal cut-off point for serum aldosterone was 83 pg/ml (sensitivity = 46%, specificity = 90%), for age it was 57 years (sensitivity = 86%, specificity = 76%).

Discussion

Although the coronary artery calcium score can significantly improve cardiovascular risk stratification (Osawa et al., 2016; De Lemos et al., 2017), it may not be

Table 2 – Odds ratios for the prediction of CACS > 0 AU and CACS > 100 AU

	CACS > 0 AU		CACS > 100 AU	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**
Univariate models				
Age (years)	1.14 (1.04–1.27)	0.01	1.22 (1.08–1.43)	0.01
Female sex (yes/no)	0.59 (0.14–2.07)	0.43	0.98 (0.27–4.09)	0.97
Smoking (yes/no)	1.09 (0.19–8.42)	0.92	0.52 (0.03–3.67)	0.58
DM (yes/no)	2.89 (0.65–20.43)	0.20	1.82 (0.41–7.28)	0.40
BMI (kg/m^2)	1.07 (0.99–1.17)	0.10	1.02 (0.94–1.10)	0.68
SBP (mm Hg)	1.00 (0.97–1.04)	0.86	1.01 (0.98–1.05)	0.41
DBP (mm Hg)	1.00 (0.94–1.05)	0.88	0.99 (0.93–1.05)	0.81
TC (mmol/l)	0.84 (0.48–1.44)	0.52	0.75 (0.39–1.37)	0.37
eGFR (ml/min)	0.04 (0.00–1.12)	0.07	0.50 (0.02–14.86)	0.68
Serum aldosterone (10 pg/ml)	1.02 (0.92–1.16)	0.68	1.18 (1.05–1.35)	0.01
Multivariate model				
Age (years)	–	–	1.20 (1.06–1.41)	0.01
Serum aldosterone (10 pg/ml)	–	–	1.16 (1.02–1.34)	0.03

CACS – coronary artery calcium score; AU – Agatston units; OR – odds ratio; CI – confidence interval; DM – diabetes mellitus; BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure; TC – total cholesterol; eGFR – estimated glomerular filtration rate

Table 3 – Estimations of accuracy, distinguishing ability and calibration of the models for prediction CACS > 0 AU and CACS > 100 AU

		Mean Brier score	AUC (CI)	H-L test
CACS > 0 AU	Age	0.20	0.75 (0.62–0.89)	–
CACS > 100 AU	Age	0.16	0.80 (0.67–0.93)	–
	Aldosterone	0.16	0.72 (0.56–0.88)	0.67
	Age + aldosterone	0.14	0.83 (0.70–0.95)	0.81

CACS – coronary artery calcium score; AU – Agatston units; AUC – area under the curve; CI – confidence interval; H-L test – Hosmer-Lemeshow goodness-of-fit test (p-value). P-values for the comparison of the AUCs using method by DeLong et al. (1988): age vs. aldosterone – p=0.39; age vs. age + aldosterone – p=0.36; aldosterone vs. age + aldosterone – p=0.16

affordable for low and middle income countries (Mancia et al., 2013; Zhao et al., 2014). Therefore, a cheaper measure, such as serum aldosterone, to predict the coronary artery calcium score is needed. Findings of this single-center study from Ukraine indicate that aldosterone could predict CACS > 100 AU in patients with CKD. However, aldosterone was not a better predictor than age alone.

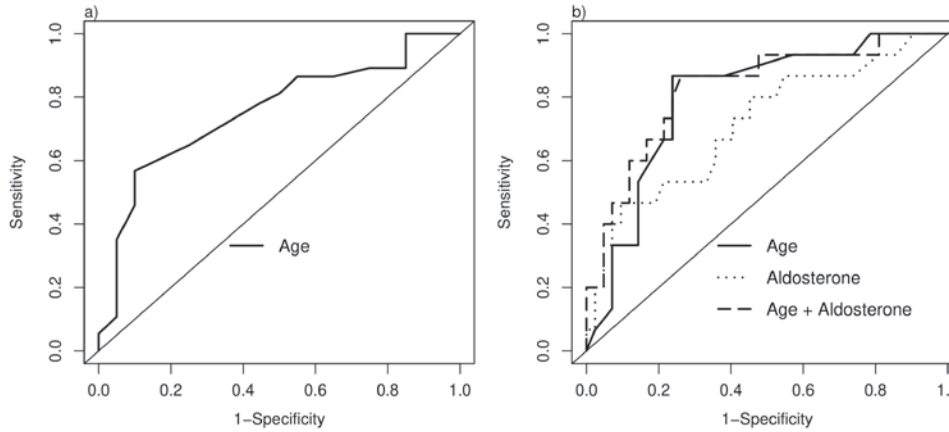

Figure 1 – Receiver operating characteristic curves for the prediction of CACS (coronary artery calcium score) > 0 AU (Agatston units) (a) and CACS > 100 AU (b).

Coronary artery calcium score in the prediction of cardiovascular events

CACS implementation has clear benefits: it is a highly reproducible test, it is non-invasive, fast and simple in performance and its added value to standard cardiovascular risk prediction tools is the greatest among other proposed risk factors (Mancia et al., 2013; Zhao et al., 2014). At the same time, the equipment for CACS may not be available in low and middle income countries, and this equipment requires qualified operators (Zhao et al., 2014). In low resource settings, new diagnostic tools are concentrated in the clinics of big administrative centers, rather than in small clinics (Vedanthan et al., 2014). Governments usually cover only a limited number of investigations, while the fee for the access to a new diagnostic tool may be too high for the majority of the patients (Vedanthan et al., 2014; Zhao et al., 2014). The cost-effectiveness of CACS is a matter of debate (Van Kempen et al., 2011; Mancia et al., 2013; Pletcher, 2016). In the 2013 European Society of Hypertension/European Society of Cardiology Guidelines for the management of arterial hypertension, CACS received the lowest possible grade for cost-effectiveness (Mancia et al., 2013), and there is concern whether it should be recommended for asymptomatic women (Van Kempen et al., 2011; Pletcher, 2016). However, coronary artery calcium scoring in certain populations could allow improvement of outcomes. In asymptomatic individuals, CACS > 100 AU may be regarded as an indication for reclassifying of their cardiovascular risk into a higher grade with the corresponding revision of treatment (Mach et al., 2020). For symptomatic patients, a negative CACS indicates a low probability of obstructive coronary artery disease (Knuuti et al., 2020). Finally, it may be suggested that the interpretation of CACS results for CKD patients should be different from the general population. CACS in CKD patients may be influenced by the calcification

of the medial layer of coronary arteries and, therefore, reflect non-obstructive atherosclerosis (Chen et al., 2017).

Aldosterone in the prediction of cardiovascular events

Aldosterone may be a promising and cheap alternative predictor of cardiovascular events due to the presence of a likely causal relationship between aldosterone and cardiovascular complications (Donderski et al., 2017). The majority of patients with CKD do not die from CKD-related causes of death, but rather die from cardiovascular complications (Thompson et al., 2015). High cardiovascular mortality in CKD patients is related to the rapid development of atherosclerosis, which pathogenesis in CKD is complex (Valdivielso et al., 2019). The development of atherosclerosis in CKD may be influenced by additional (non-classical) cardiovascular risk factors such as low-grade inflammation, mineral and bone disorder and fluid overload (Valdivielso et al., 2019). Aldosterone can be regarded as the factor that participates in all the mentioned pathways (Donderski et al., 2017). However, its measurement may be suggested only in CKD, which is usually accompanied by aldosterone excess or mineralocorticoid receptor activation (Donderski et al., 2017). Unlike other proposed additional markers of cardiovascular events (Osawa et al., 2016; Chen et al., 2018), aldosterone, may be also a treatment target. The involvement of aldosterone in multiple pathways of atherosclerosis progression and availability of aldosterone antagonists (Funder, 2017) provide a good reason for testing aldosterone in routine clinical practice for patients with CKD.

So far it was unclear to what extent aldosterone can be used for cardiovascular risk assessment in patients with CKD. The results of our study now show that aldosterone could predict CACS > 100 AU, but could not predict CACS > 0 AU. In our study the optimal cut-off point for aldosterone in prediction of CACS > 100 AU (83 pg/ml) was found to be close to the threshold for diagnosing high aldosterone in Ukrainian guidelines – 90 pg/ml (Mostovoy and Sidorov, 2016). However, the sensitivity of this optimal cut-off point was 46%, which indicates that more than a half of patients with aldosterone below 83 pg/ml would be falsely classified as having CACS < 100 AU. Therefore, aldosterone measurement may not be recommended in routine clinical practice for prediction of CACS > 100 AU and reassessment of cardiovascular risk in the patients with CKD (Mach et al., 2020).

Moreover, according to results of our study, aldosterone was not a better predictor of CACS than age. In our study age was a significant predictor of both CACS > 100 AU and CACS > 0 AU. Both models for prediction of CACS by age showed that the optimal cut-off point was 57 years. In our study, the optimal cut-off point for age in the prediction of CACS > 100 AU had good sensitivity (86%) and specificity (76%), which allow to consider it for usage in routine clinical practices. The optimal cut-off points for age in our study were close to the age of 55 years, after which changes in treatment may be considered for asymptomatic persons (according

to the 2019 American College of Cardiology/American Heart Association Guideline on the Primary Prevention of Cardiovascular Disease) (Arnett et al., 2019).

Several important remarks needed to be made. First, the population of patients with CKD in Ukraine is much younger compared to other European countries (Kramer et al., 2019). Second, although age is known to be a powerful cardiovascular risk factor (D'Agostino et al., 2008; Piepoli et al., 2016), age alone may not be sufficient for a good discrimination of patients' risk. In the countries that use the same variables for cardiovascular risk stratification (including age), mortality rates differ dramatically (Timmis et al., 2018). Therefore, cardiovascular risk assessment tools that are supposed to have a high predictive value in high income countries may not be generalizable to low-income countries and vice versa. It was hypothesized that aldosterone may improve the prognostic ability of age-based models for cardiovascular risk stratification. However, our study shows that aldosterone neither was better than age in the prediction of CACS, nor did it improve the prediction of CACS by age in CKD patients in Ukraine.

Strengths and limitations

A main strength of this study is the availability of both data on CACS and aldosterone in patients with CKD from an Eastern European country with high cardiovascular mortality (Timmis et al., 2018) and early development of chronic kidney disease (Kramer et al., 2019). This study also has several limitations. One of the main limitations is the small sample size. Results of this study need to be confirmed in a study with a larger sample and external validation is needed. Simultaneous evaluation of serum renin was not performed, therefore differentiation between primary and secondary causes of aldosterone level elevation was not possible. In addition, data about serum aldosterone prior to the start of ACEi/ARB therapy was missing. Therefore, it was impossible to determine whether aldosterone elevation was related to the start of antihypertensive treatment (the aldosterone "breakthrough" phenomenon). The study sample included patients with CKD, and some of the patient had CKD related to systemic sclerosis (n=13). The pathogenesis of organ damage in systemic sclerosis is unique (includes inflammation, excessive fibrosis and vasculopathy) (Orlandi et al., 2018), which could influence the results of the study. However, patients with systemic sclerosis in our study had a stable course of the disease with controlled inflammation and did not receive methotrexate. Also, there was no significant difference in the distribution of sex, age, eGFR, CACS > 0 AU, and CACS > 100 AU between patients with and without systemic sclerosis.

Conclusion

Findings of our study in a sample of CKD patients from a single center in Ukraine suggest that aldosterone was a significant predictor of CACS > 100 AU, but aldosterone was not a better predictor than age. Our findings need to be confirmed

in a larger external sample. Results of this study may be useful for clinicians, who could use age for the assessment of atherosclerosis progression in CKD patients, when CACS is not available. Our study highlights the need for the development of risk assessment tools tailored to local populations with CKD and to the economic resources of healthcare systems.

References

Arnett, D. K., Blumenthal, R. S., Albert, M. A., Buroker, A. B., Goldberger, Z. D., Hahn, E. J., Himmelfarb, C. D., Khera, A., Lloyd-Jones, D., McEvoy, J. W., Michos, E. D., Miedema, M. D., Muñoz, D., Smith, S. C., Virani, S. S., Williams, K. A., Yeboah, J., Ziaeian, B. (2019) 2019 ACC/AHA Guideline on the primary prevention of cardiovascular disease: Executive summary: A report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. *Circulation* **140(11)**, e563–e595.

Chen, J., Budoff, M. J., Reilly, M. P., Yang, W., Rosas, S. E., Rahman, M., Zhang, X., Roy, J. A., Lustigova, E., Nessel, L., Ford, V., Raj, D., Porter, A. C., Soliman, E. Z., Wright, J. T. Jr., Wolf, M., He, J.; CRIC Investigators (2017) Coronary artery calcification and risk of cardiovascular disease and death among patients with chronic kidney disease. *JAMA Cardiol*. **2(6)**, 635–643.

Chen, S.-C., Huang, J.-C., Su, H.-M., Chiu, Y.-W., Chang, J.-M., Hwang, S.-J., Chen, H.-C. (2018) Prognostic cardiovascular markers in chronic kidney disease. *Kidney Blood Press. Res.* **43(4)**, 1388–1407.

D'Agostino, R. B., Vasan, R. S., Pencina, M. J., Wolf, P. A., Cobain, M., Massaro, J. M., Kannel, W. B. (2008) General cardiovascular risk profile for use in primary care: The Framingham heart study. *Circulation* **117(6)**, 743–753.

De Lemos, J. A., Ayers, C. R., Levine, B., DeFilippi, C. R., Wang, T. J., Hundley, W. G., Berry, J. D., Seliger, S. L., McGuire, D. K., Ouyang, P., Drazner, M. H., Budoff, M., Greenland, P., Ballantyne, C. M., Khera, A. (2017) Multimodality strategy for cardiovascular risk assessment: Performance in 2 population-based cohorts. *Circulation* **135(22)**, 2119–2132.

DeLong, E. R., DeLong, D. M., Clarke-Pearson, D. L. (1988) Comparing the areas under two or more correlated receiver operating characteristic curves: A nonparametric approach. *Biometrics* **44(3)**, 837–845.

Donderski, R., Stróżecki, P., Sulikowska, B., Grajewska, M., Miśkowiec, I., Stefańska, A., Siódmiak, J., Odrowąż-Sypniewska, G., Manitius, J. (2017) Aldosterone antagonist therapy and its relationship with inflammation, fibrosis, thrombosis, mineral-bone disorder and cardiovascular complications in peritoneal dialysis (PD) patients. *Int. Urol. Nephrol.* **49(10)**, 1867–1873.

Eknoyan, G., Lameire, N., Echardt, K., Kasiske, B., Wheeler, D. (2013) KDIGO 2012 Clinical Practice Guideline for the evaluation and management of chronic kidney disease. *Kidney Int. Suppl.* **3(1)**, 1–150.

Firke, S. (2020) *janitor: Simple Tools for Examining and Cleaning Dirty Data* (R package version 1.2.1). Available at: https://CRAN.R-project.org/package=janitor

Funder, J. W. (2017) Spironolactone in cardiovascular disease: An expanding universe? *F1000Res.* **6**, 1738.

Güder, G., Bauersachs, J., Frantz, S., Weismann, D., Allolio, B., Ertl, G., Angermann, C. E., Störk, S. (2007) Complementary and incremental mortality risk prediction by cortisol and aldosterone in chronic heart failure. *Circulation* **115(13)**, 1754–1761.

Hayashi, K., Suzuki, T., Sakamaki, Y., Ito, S. (2018) Cardiac hypertrophy in chronic kidney disease – Role of aldosterone and FGF23. *Ren. Replace. Ther.* **4(1)**, 10.

Judd, E., Calhoun, D. A. (2015) Management of hypertension in CKD: Beyond the guidelines. *Adv. Chronic Kidney Dis.* **22(2)**, 116–122.

Knuuti, J., Wijns, W., Saraste, A., Capodanno, D., Barbato, E., Funck-Brentano, C., Prescott, E., Storey, R. F., Deaton, C., Cuisset, T., Agewall, S., Dickstein, K., Edvardsen, T., Escaned, J., Gersh, B. J., Svitil, P., Gilard, M., Hasdai, D., Hatala, R., Mahfoud, F., Masip, J., Muneretto, C., Valgimigli, M., Achenbach, S., Bax, J. J.; ESC Scientific Document Group (2020) 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur. Heart J.* **41(3)**, 407–477.

Kobayashi, M., Stienen, S., Maaten, J. M., Dickstein, K., Samani, N. J., Lang, C. C., Ng, L. L., Anker, S. D., Metra, M., Preud'homme, G., Duarte, K., Lamiral, Z., Girerd, N., Rossignol, P., Veldhuisen, D. J., Voors, A. A., Zannad, F., Ferreira, J. P. (2020) Clinical determinants and prognostic implications of renin and aldosterone in patients with symptomatic heart failure. *ESC Heart Fail.* **7(3)**, 953–963.

Kramer, A., Pippias, M., Noordzij, M., Stel, V. S., Andrusev, A. M., Aparicio-Madre, M. I., Arribas Monzón, F. E., Åsberg, A., Barbullushi, M., Beltrán, P., Bonthuis, M., Caskey, F. J., Castro de la Nuez, P., Cernevskis, H., De Meester, J., Finne, P., Golan, E., Heaf, J. G., Hemmelder, M. H., Ioannou, K., Kantaria, N., Komissarov, K., Korejwo, G., Kramar, R., Lassalle, M., Lopot, F., Macário, F., Mackinnon, B., Pálsson, R., Pechter, Ü., Piñera, V. C., Santiuste de Pablos, C., Segarra-Medrano, A., Seyahi, N., Slon Roblero, M. F., Stojceva-Taneva, O., Vazelov, E., Winzeler, R., Ziginskiene, E., Massy, Z., Jager, K. J. (2019) The European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) Registry Annual Report 2016: A summary. *Clin. Kidney J.* **12(5)**, 702–720.

Lele, S. R., Keim, J. L., Solymos, P. (2019) *ResourceSelection: Resource Selection (Probability) Functions for Use-Availability Data* (R package version 0.3-5). Available at: https://CRAN.R-project.org/package=ResourceSelection

López-Ratón, M., Rodríguez-Álvarez, M. X., Suárez, C. C., Sampedro, F. G. (2014) OptimalCutpoints: An R package for selecting optimal cutpoints in diagnostic tests. *J. Stat. Softw.* **61(8)**, 1–36.

Mach, F., Baigent, C., Catapano, A. L., Koskinas, K. C., Casula, M., Badimon, L., Chapman, M. J., De Backer, G. G., Delgado, V., Ference, B. A., Graham, I. M., Halliday, A., Landmesser, U., Mihaylova, B., Pedersen, T. R., Riccardi, G., Richter, D. J., Sabatine, M. S., Taskinen, M. R., Tokgozoglu, L., Wiklund, O.; ESC Scientific Document Group (2020) 2019 ESC/EAS Guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk. *Eur. Heart J.* **41(1)**, 111–188.

Mancia, G., Fagard, R., Narkiewicz, K., Redon, J., Zanchetti, A., Böhm, M., Christiaens, T., Cifkova, R., De Backer, G., Dominiczak, A., Galderisi, M., Grobbee, D. E., Jaarsma, T., Kirchhof, P., Kjeldsen, S. E., Laurent, S., Manolis, A. J., Nilsson, P. M., Ruilope, L. M., Schmieder, R. E., Sirnes, P. A., Sleight, P., Viigimaa, M., Waeber, B., Zannad, F.; Task Force Members (2013) 2013 ESH/ESC guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur. Heart J.* **34(28)**, 2159–2219.

Matsushita, K., Ballew, S. H., Coresh, J. (2016) Cardiovascular risk prediction in people with CKD. *Curr. Opin. Nephrol. Hypertens*. **25(6)**, 518–523.

Moran, A. E., Forouzanfar, M. H., Roth, G. A., Mensah, G. A., Ezzati, M., Murray, C. J. L. (2014) Temporal trends in ischemic heart disease mortality in 21 world regions, 1980 to 2010: The Global Burden of Disease 2010 Study. *Circulation* **129(14)**, 1483–1492.

Mostovoy, Y. M., Sidorov, O. O. (2016) *Laboratory Tests. Normal Values, Interpretation of Changes*. Center DZK.

Orange Health Consultants (2018) *Health Care in Ukraine*. Commissioned by the Netherlands Enterprise Agency.

Orlandi, M., Barsotti, S., Lepri, G., Codullo, V., Battista, M. D., Guiducci, S., Rossa, A. D. (2018) One year in review 2018: Systemic sclerosis. *Clin. Exp. Rheumatol.* **113(4)**, 3–23 (Suppl. 36).

Osawa, K., Nakanishi, R., Budoff, M. (2016) Coronary artery calcification; report from the Multi-Ethnic Study of Atherosclerosis. *Glob. Heart* **11(3)**, 287–293.

Piepoli, M. F., Hoes, A. W., Agewall, S., Albus, C., Brotons, C., Catapano, A. L., Cooney, M. T., Corrà, U., Cosyns, B., Deaton, C., Graham, I., Hall, M. S., Hobbs, F. D. R., Løchen, M. L., Löllgen, H., Marques-Vidal, P., Perk, J., Prescott, E., Redon, J., Richter, D., Sattar, N., Smulders, Y., Tiberi, M., van der Worp, H. B., van Dis, I., Verschuren, W. M. M., Binno, S.; ESC Scientific Document Group (2016) 2016 European Guidelines on cardiovascular disease prevention in clinical practice. *Eur. Heart J.* **37(29)**, 2315–2381.

Pletcher, M. (2016) *When Is Measuring a Coronary Artery Calcium Score Cost Effective?* American College of Cardiology. Available at: https://www.acc.org/latest-in-cardiology/articles/2016/06/14/09/17/when-is-measuring-a-coronary-artery-calcium-score-cost-effective

R Core Team (2020) *R: A Language and Environment for Statistical Computing* (3.6.3) [R]. R Foundation for Statistical Computing. Available at: https://www.R-project.org/

Robin, X., Turck, N., Hainard, A., Tiberti, N., Lisacek, F., Sanchez, J.-C., Müller, M. (2011) pROC: An open-source package for R and S+ to analyze and compare ROC curves. *BMC Bioinformatics* **12(1)**, 77.

Schrier, R. W. (2010) Aldosterone "escape" vs "breakthrough". *Nat. Rev. Nephrol.* **6(2)**, 61.

Sing, T., Sander, O., Beerenwinkel, N., Lengauer, T. (2005) ROCR: Visualizing classifier performance in R. *Bioinformatics* **21(20)**, 7881.

Thompson, S., James, M., Wiebe, N., Hemmelgarn, B., Manns, B., Klarenbach, S., Tonelli, M. (2015) Cause of death in patients with reduced kidney function. *J. Am. Soc. Nephrol.* **26(10)**, 2504–2511.

Timmis, A., Townsend, N., Gale, C., Grobbee, R., Maniadakis, N., Flather, M., Wilkins, E., Wright, L., Vos, R., Bax, J., Blum, M., Pinto, F., Vardas, P.; ESC Scientific Document Group (2018) European Society of Cardiology: Cardiovascular disease statistics 2017. *Eur. Heart J.* **39(7)**, 508–579.

Valdivielso, J. M., Rodríguez-Puyol, D., Pascual, J., Barrios, C., Bermúdez-López, M., Sánchez-Niño, M. D., Pérez-Fernández, M., Ortiz, A. (2019) Atherosclerosis in chronic kidney disease: More, less, or just different? *Arterioscler. Thromb. Vasc. Biol.* **39(10)**, 1938–1966.

Van Kempen, B. J. H., Spronk, S., Koller, M. T., Elias-Smale, S. E., Fleischmann, K. E., Ikram, M. A., Krestin, G. P., Hofman, A., Witteman, J. C. M., Hunink, M. G. M. (2011) Comparative effectiveness and cost-effectiveness of computed tomography screening for coronary artery calcium in asymptomatic individuals. *J. Am. Coll. Cardiol.* **58(16)**, 1690–1701.

Vedanthan, R., Choi, B. G., Baber, U., Narula, J., Fuster, V. (2014) Bioimaging and subclinical cardiovascular disease in low- and middle-income countries. *J. Cardiovasc. Transl. Res.* **7(8)**, 701–710.

Whelton, P. K., Carey, R. M., Aronow, W. S., Ovbiagele, B., Casey, D. E., Smith, S. C., Collins, K. J., Spencer, C. C., Himmelfarb, C. D., Stafford, R. S., Depalma, S. M., Taler, S. J., Gidding, S., Thomas, R. J., Jamerson, K. A., Williams, K. A., Jones, D. W., Williamson, J. D., Maclaughlin, E. J., Muntner, P., Ovbiagele, B., Smith, S. C., Spencer, C. C., Stafford, R. S., Taler, S. J., Thomas, R. J., Williams, K. A., Williamson, J. D., Wright, J. T. (2018) 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: Executive summary: A report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. *Hypertension* **71(6)**, 1269–1324.

Williams, B., Mancia, G., Spiering, W., Agabiti Rosei, E., Azizi, M., Burnier, M., Clement, D., Coca, A., de Simone, G., Dominiczak, A., Kahan, T., Mahfoud, F., Redon, J., Ruilope, L., Zanchetti, A., Kerins, M., Kjeldsen, S. E., Kreutz, R., Laurent, S., Lip, G. Y. H., McManus, R., Narkiewicz, K., Ruschitzka, F., Schmieder, R. E., Shlyakhto, E., Tsioufis, C., Aboyans, V., Desormais, I.; ESC Scientific Document Group (2018) 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur. Heart J.* **39(33)**, 3021–3104.

Zhao, Y., Malik, S., Wong, N. D. (2014) Evidence for coronary artery calcification screening in the early detection of coronary artery disease and implications of screening in developing countries. *Glob. Heart* **9(4)**, 399.