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ADMA and C-reactive protein as mortality predictors in dialysis patients

Research Article

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Abstract: There is a higher mortality between patients with end-stage renal disease than patients in the general population. These circumstances have led to a search for risk factors as predictors of mortality in dialysis patients. Amongst those, inhibitors of the nitric-oxide (NO) synthesis deserve special attention, since patients with end-stage renal disease are also characterized by accelerated atherosclerosis. Asymmetric-dimethylarginine (ADMA) and symmetric-dimethylarginine (SDMA), as well as C-reactive protein (CRP), have also been recognized as predictors of mortality in patients on dialysis. The aim of our study was to compare the prediction power of ADMA, SDMA and CRP for all-cause mortality in patients with end stage renal disease during the fourteen month follow-up. In total 162 patients on hemodialysis were included. ADMA and SDMA were measured by the high-performance liquid chromatography (HPLC); CRP was measured using immunonephelometric assays. During the 14-month period 28 patients (34.1%) died from all-cause mortality. Using univariate analysis, hazard ratios (HR) of the potential independent predictors of mortality in hemodialysis patients were ADMA (HR 1.39 (1.01-1.91) p=0.043) and CRP (HR 1.024 (1.009-1.1.040) p=0.001). Further, multivariate analysis (MVA), however, showed that ADMA is the only predictor of all-cause mortality (HR 1.76 (1.002-3.11) P=0.049), while SDMA failed to predict death in this population. Therefore, our data shows that ADMA is an independent and better marker of all-cause mortality compared with CRP.

Keywords: *Asymmetric-dimethylarginine • Symmetric-dimethylarginine • C-reactive protein • Dialysis • Mortality prediction*

1. Introduction

Despite constant improvements in dialysis technology and renal care, there is still a high mortality rate amongst patients on hemodialysis. Patients with the end-stage renal disease (ESRD) have 10-20 fold higher mortality due to cardiovascular diseases (CVD) than the patients in general population [1,2]. These circumstances have led to the research of traditional as well as nontraditional risk factors which are potential predictors of mortality in patients on dialysis. Among numerous risk factors, inhibitors of nitric-oxide (NO) synthesis deserve particular attention, because ESRD patients are prone to develop accelerated atherosclerosis [3]. Asymmetric-dimethylarginine (ADMA) is derived largely from the degradation of proteins containing methylated arginine residues and it has been recognized as unique endogenous competitive inhibitor of nitric-oxide synthase. Therefore, ADMA may influence nitric oxide (NO) production and may be responsible for vasodilatation and regulation of the systematic pressure and local blood flow. Approximately 20% of ADMA is cleared

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out by the kidney, whereas the rest gets metabolized by the enzyme dimethylarginine dimethylaminohydrolase (DDAH).

Previous studies have shown the enhancement of ADMA plasma levels in pathological conditions is characterized by strong presence of oxidative stress, like that in kidney failure and diabetes [4]. Patients with renal failure have elevated levels of ADMA compared with healthy ones [5]. In particular, ADMA levels were elevated more in the patients undergoing hemodialysis than in the ones undergoing peritoneal dialysis. Results from this study suggested that patients on hemodialysis are more prone to inflammation and/or oxidative stress [6]. According to Zoccali et al. [7], there are four mechanisms that may explain increased level of ADMA: increased methylation of proteins, increased protein turnover, reduced DDAH activity and impaired renal excretion. It is well documented that plasma ADMA concentration is associated with carotid intima-thickness [8,9], left ventricular hypertrophy as well as cardiovascular complications [10]. Several studies have confirmed that ADMA is an independent predictor of all-cause mortality and CVD mortality in patients with ESRD [11] and peripheral arterial disease [12]. Recently, it was reported that circulating levels of ADMA correlate independently with the measures of disease severity and major adverse cardiovascular events [13]. Moreover, ADMA could have a metabolic role tightly related to the development of systemic inflammatory reaction. For example, ADMA plasma level in severe sepsis/septic shock is largly increased due to systemic inflammatory response and organ failure [14]. High ADMA is not only a risk predictor, but it contributes to the adverse events interfering with nitric oxide fine tuning of the microcirculation involving the endothelium, platelets and white blood cells.

SDMA was initially considered an inactive isomer of ADMA, when it was shown to correlate with the glomerular filtration rate [15]; nowadays SDMA is considered a marker of GFR and a marker of the extent of coronary artery disease [16].

Dialysis is a state of chronic inflammation. Stimuli that lead to the development of chronic inflammatory state are: low-grade infection, repeated exposure to dialysis filters [17], and auto-oxidation products. As a result of those processes, the levels of C-reactive protein (CRP) increase in the body. CRP is considered a powerful risk factor for the development of CVD and the most important predictor of cardiovascular mortality, both in general population and in patients with the end-stage renal disease [18,19]. Although it has been shown that interleukin 6 (IL-6) is a stronger predictor of above mortality than CRP [20,21], it appears that determination of CRP levels is nevertheless more reliable and cost-effective in everyday practice.

Despite lacking the exact explanation for the high mortality of haemodialysis patients, there is still a need for their risk stratification and a better management. ADMA, SDMA and CRP were chosen as markers because they covered wide range of pathophysiological processes, which contribute to the development and progression of atherosclerosis. Considering this pathophysiological background, the aim of the present study was to compare the prediction power of ADMA and CRP for all-cause mortality with the cardiovascular outcomes in patients with ESRD, during the fourteen months follow-up study.

2. Methods

This follow-up study comprised 162 (116 males and 46 females) patients on hemodialysis with ESRD, and 30 healthy controls. The causes of ESRD in the hemodialysis patients were chronic glomerulonephritis (n=38), tubulointerstitial nephritis (n=22), polycystic kidney disease (n=20), nephrosclerosis (n=24), diabetic nephropathies (n=20), hypertension (n=32) and other (n=8). Hypertension was diagnosed if the systolic and/or diastolic blood pressure exceeded 140 and/or 90 mmHg or if there was a history of hypertension, evident through the use of antihypertensive drugs. Body mass index was recorded in all patients.

All patients were dialyzed three times per week using bicarbonate-based solution and polyamide and polysulphone low-flux or high-flux membranes. Fasting blood samples were collected after 20 to 30 min of quiet resting in the semirecumbent position before the midweek dialysis session. Mean duration of dialysis was 93.07±65.20 months (range 24 - 312 months). There was no significant difference in the duration of dialysis between alive patients and those who died along the way (respectively, 96 ± 67.98, 78.86 ± 49.08, P=0.279, 28 died and 134 survived). Plasma concentration of ADMA was measured by the high-performance liquid chromatography-HPLC (Agilent 1200 Series) and precolumn derivatization with o-phthaldialdehyde (OPA), as described previously [22,23]. Breefly: plasma (0.2 mL) with added monomethylarginine as an internal standard (IS) (50 µL; 10 µM) was applied to a mixed-mode cation-exchange SPE cartridge (Supelco Discovery® DSC-MCAX, 100 mg/mL, Supelco, Bellefonte, PA USA) previously activated with methanol (1 mL) and TCA 2% (2 mL). After the column washing (TCA 2%, 150 mmol/L phosphate buffer pH 8.0, methanol), the aminoacids were

eluted with 1.2 mL of 2% triethylamine (TEA) solution in methanol:water; 70:30; v:v). The eluate was dried under nitrogen (50°C), redissolved in 0.4 mL starting buffer solution and derivatized with OPA (ortho-phthaldialdehyde) reagent (0.1 mL, 2 min, 25°C) before subsequent analysis. The HPLC was equipped with a fluorescent detector (λex 340 nm, λem 445 nm; PMT gain was 14 between 3 and 5.20 min) and a Zorbax SB-C18 column (150 x 4.6 mm, 3.5 µm). The baseline separation of the methylated arginines was achieved using gradient between mobile phase A (sodium phosphate buffer, 40 mmol/L, pH 6.2) and B (deionised water: methanol; 1:9; v:v). The analysis started at 35% of phase B and held for 5.0 min; than it was increased linearly to 100% over 0.5 min and column was washed for up to 8.5 min before reconditioning (total run time: 10 min).

C-reactive protein (CRP) was measured using immunonephelometric assays (Olympus AU400). Serum cholesterol, triglycerides, urea, creatinine, proteins and albumins measurements were obtained using standard clinical laboratory methods and analysis performed automated on BioSystems A25 analyzer (Barcelona, Spain). After the initial assessment, patients were followed up during the fourteen months period. No patient has died during the follow-up. The study was approved by the ethics committee of Faculty of Medicine, University of Niš (number 01-890-5) and all patients have provided informed consent.

3. Statistical analysis

All data are presented as mean ± standard deviation (SD), median and interquartile range, or percent frequency. All comparisons between groups were made using Students t-test, Mann-Whitney or Chi Square test. Survival curves were estimated using Kaplan-Meier method and the differences were assessed with the log-rank test. The relationships between ADMA, CRP, SDMA and all-cause mortality were investigated using univariate and multiple Cox regression analyses. For the latter analysis all investigated parameters were adjusted for age, sex and smoking. Hazard ratio (HR) and confidence interval (95% CI) are presented per 1-SD change in ADMA levels. Receiver operating characteristic (ROC) curve analysis was conducted to determine the optimal threshold with maximum combination of specificity and sensitivity in predicting mortality. Statistical analyses were done using SPSS package v16.0 for Windows. P <0.05 was considered statistically significant.

4. Results

The baseline characteristics of the study population are summariezed in Table 1. Concentrations of ADMA, SDMA, SAA and CRP were statistically higher in ESRD patients then in healthy controls.

Table 1. Baseline characteristics for ESRD patients on hemodialysis and healthy controls.

	Patients n=162	Controls n=30	p
Age	59.52±10.97	57.19±9.71	0.278
Sex (male/female)	110/52	17/13	0.325
Current tobacco use	30	6	0.949
History of diabetes	23	4	0.582
Hypertension	91	12	0.152
BMI	24.62±3.41	23.49±3.92	0.105
ADMA	0.38±0.21	0.26±0.11	0.002
SDMA (µmol/L)	0.749±0.224	0.938±0.233	<0.001
CRP (mg/L)	8.33±9.06	12.71±35.04	0.171
SAA	3.6±4.13	1.43±0.71	0.005
Total cholesterol (mmol/L)	3.72±0.88	5.53±0.71	0.001
Triglycerides (mmol/L)	2.34±1.51	1.87±0.87	0.101
Urea (mmol/L)	32.75±26.23	5.14±0.80	<0.001
Creatinine (µmol/L)	911.76±226.55	69.79±15.26	<0.001
Proteins (g/L)	66.81±10.41	69.22±0.5	0.207
Albumins (g/L)	33.36±6.23	39.86±2.12	<0.001
Haemoglobin (g/dL)	111,70±16,23	142,32±16,46	<0.001

Demographic, clinical and laboratory characteristics of the patients classified by ADMA tertiles are presented in Table 2. In 13% of total patients there was history of diabetes, 10% had history of CVD at baseline, and 12% were habitual smokers. Levels of ADMA were 0.38 ± 0.21 µmol/L (range of 0.10 - 1.64 µmol/L), and those of SDMA were 0.96 ± 0.42 µmol/L (range 0.44 - 2.97 µmol/L). The mean concentration of CRP was 8.49 ± 16.21 µmol/L. Plasma ADMA and SDMA concentrations correlated with each other (r=0.59, P<0.001). SDMA was directly related to BMI (r=0.40, P=0.027), and indirectly related to levels of hemoglobin (r= -0.12, P=0.030).

During the 14-month period, 28 patients (34.1%) died from all-cause mortality. Concentrations of ADMA and CRP were statistically higher in patients who died than in the still alive patients (respectively, ADMA: 0.36(0.28-0.48), 0.32(0.25-0.40), P=0.035, CRP: 6.85(3.25-31.88), 3.2(1.2-7.7), P=0.027 Figure 1) but this was not the case with SDMA (respectively, 0.88(0.59-1.05), 0.88(0.66-1.36), P=0.099).

ROC curve analysis revealed relationship between ADMA, SDMA, CRP and all-cause mortality. The areas

Table 2. Baseline characteristics of the patients by tertiles of ADMA (μmol/L).

	Tertile 1 (0.11 to 0.29) n=54	Tertile 2 (0.29 to 0.39) n=54	Tertile 3 (0.39 to 1.64) n=54	p
Age	59.52±10.97	58.19±10.87	57.37±12.58	0.884
Male	42	38	36	0.654
Female	12	16	18	
Current tobacco use	8	4	8	0.402
History of diabetes	10	4	6	0.450
BMI	24.62±3.41	23.49±3.92	26.12±4.31	0.624
CRP (mg/L)	8.33±9.06	12.71±35.04	16.7±27.14	0.615
SDMA(μmol/L)	0.749±0.224	0.938±0.233	1.203±0.567	P<0.001***
Total cholesterol (mmol/L)	3.58±0.81	3.63±0.80	4.02±1.01	0.405
Triglycerides(mmol/L)	2.15±1.24	2.22±1.14	2.82±2.13	0.589
Urea(mmol/L)	29.38±6.42	39.10±52.28	29.99±10.52	0.808
Creatinine(μmol/L)	952.04±470.9	873.08±135.56	962.12±361.49	0.399
Proteins(g/L)	69.19±7.73	66.79±8.00	63.28±16.39	0.378
Albumins(g/L)	32.95±2.47	35.23±9.75	31.48±1.84	0.032*

Data are mean ± SD, or percent frequency, as appropriate.
** P<0.05, ***P<0.001 – first vs last tertiles*
ADMA – asymmetric-dimethylarginine, BMI – body mass index, CRP – C reactive protein.

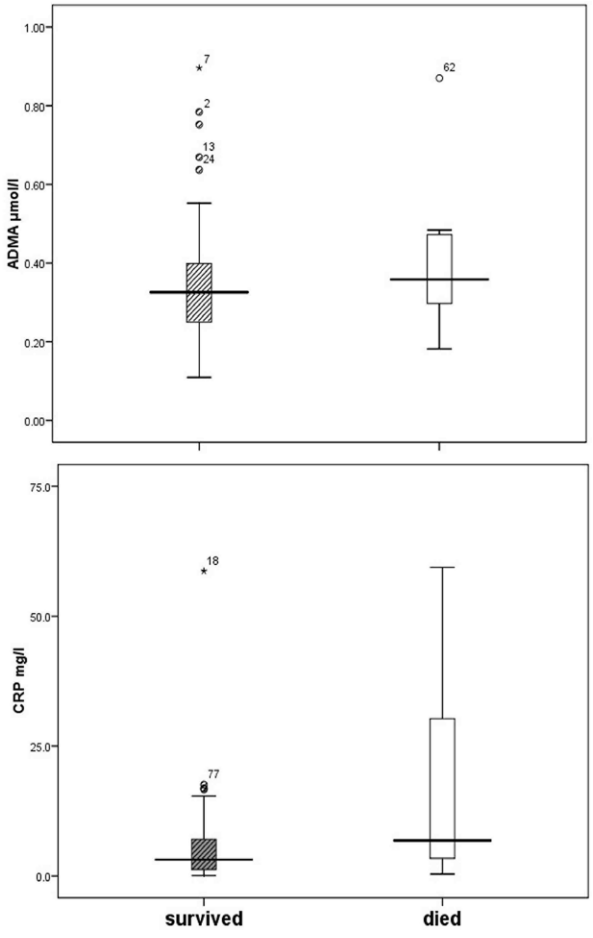

Figure 1. Plasma ADMA and CRP concentration in patients with end stage renal disease (ESRD) according to their survival after a 14 month follow-up period.

under curve were respectively, for ADMA (AUC 0.68 (0.52-0.84) P=0.035), for SDMA (AUC 0.64 (0.48-0.80) P=0.099) and for CRP (AUC 0.69 (0.52-0.86) P=0.027),. The optimal threshold of ADMA (0.383) and CRP (8.15) to predict mortality was based on combination of maximum specificity and sensitivity. Those values were close to the last tertile, hence the impact of ADMA and SDMA on mortality was analyzed in comparison with the last tertile. Kaplan Meier curve analyses showed that there is a strong association between high values of both ADMA and CRP with excess all-cause mortality (log rank=8.21, P=0.004 (Figure 2), log rank=6.74,

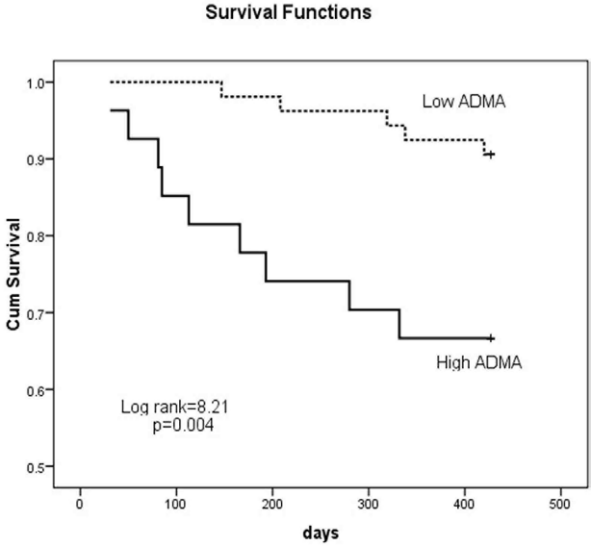

Figure 2. Kaplan-Meier survival analysis for all-cause mortality of plasma ADMA. Patients were divided into two groups: low ADMA (first and second tertiles) – dotted line; high ADMA (highest tertile) – solid line.

P=0.009 (Figure 3). Cox hazard proportional model was used to assess the prediction power of ADMA, SDMA and CRP on all-cause mortality (Table 3). Unadjusted hazard ratio showed that ADMA (HR 1.39 (1.01-1.91) P=0.043) is the strongest predictor of all-cause mortality among tested parameters. CRP is also shown as an independent predictor (HR 1.024 (1.009-1.040) P=0.001), while SDMA has shown to have no power to predict all-cause mortality (HR 1.01 (0.89-1.95) P=0.185). When Cox regression model was adjusted for age, sex, smoking and albumin, the ADMA turned out to be the only predictor of all-cause mortality (HR 1.76 (1.002-3.11) P=0.049). Further, when Cox regression model was also adjusted for age, sex, albumin, hypertension, coronary disease, history of diabetes, cholesterol and ADMA still remained the only predictor of mortality (HR 1.99 (1.02-3.87) P=0.042).

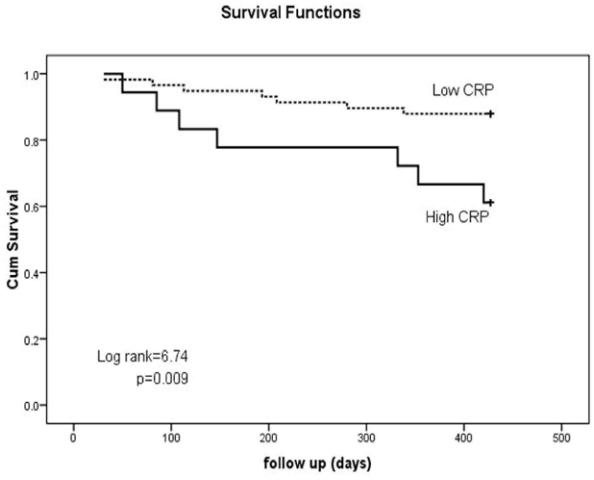

Figure 3. Kaplan-Meier survival analysis for all-cause mortality of CRP. Patients were divided into two groups: low CRP (first and second tertiles) – dotted line; high CRP (highest tertile) – solid line.

5. Discussion

In this prospective 14-month follow-up study, we show that ADMA is a stronger predictor of all-cause mortality than SDMA or CRP, in patients with the end-stage renal disease. ADMA and CRP were statistically higher in the plasm from patients who died on the way than in the still alive ones. CRP levels were elevated, although there was no sign of clinical infection or change in the leukocytes count.

This data are consistent with the study by Zoccali et al. conducted in 2001 [24], which found that any increase in concentration of ADMA by 1 µmol/L lead to an increased risk of all-cause mortality by 26%. They also suggested that ADMA may be a useful marker for atherosclerosis in general population as well as in patient on dialysis. Partially in contrast with our data, cohort study with 131 patients with chronic kidney disease showed that ADMA is an independent predictor of all-cause mortality, but CRP failed to reach statistical significant power of prediction [25]. According to these data, any increase of ADMA by 0.1 µM/L increases the risk of death by 23%. In the 5-year follow-up study, Kumagai et al. [26], showed that in comparisson with homocysteine, ADMA is a stronger predictor of cardiovascular mortality during the maintenance of hemodialysis patients.

Another study concerning the assessment of ADMA predicting power, has shown that ADMA is significantly and directly associated with the all-cause mortality (HR 2.07), but not with the cardiovascular mortality (HR 1.12) [11]. In contrast, the study on patients with chronic renal failure of different stages showed that elevated ADMA is associated with a decreased risk of cardiovascular events. This finding suggests that ADMA is a possible candidate for paradoxical epidemiology. C-reactive protein and SDMA were reported as indepen-

Table 3. Association of ADMA, SDMA and CRP with all-cause mortality.

		ADMA	SDMA	CRP
All-cause mortality	Unadjusted HR[b]	1.389	1.010	1.024
	95%CI	(1.01-1.91)	(0.88-1.95)	(1.01-1.04)
	p	0.043	0.185	0.001
	Model 1 HR	1.764	2.756	1.028
	95%CI	(1.002-3.1)	(0.65-11.74)	(1.003-1.053)
	p	0.049	0.170	0.028
	Model 2 HR	1.991	1.921	1.037
	95%CI	(1.025-3.866)	(0.453-8.141)	(0.932-1.154)
	p	0.042	0.375	0.504

Model 1 adjusted for age, sex, and smoking; Model 2 adjusted for age, sex, hypertension, coronary disease, history of diabetes, cholesterol.
HR is per 1SD of ADMA (0.20 µmol/L)
HR SDMA per 1 µmol/L increase
HR CRP per 1 mg/L increase

dent predictors of death. The levels of CRP were almost two times higher than those observed in our study, and hazard ratio was three times higher. Concentration of SDMA was almost three times higher than what our data is showing [27].

Although there are studies showing that elevated ADMA levels are associated with the increased risk of all-cause and cardiovascular mortality, thus far there has been no explanation of the nature of this process. In physiological conditions, methylarginine is synthesized by protein arginine methyltransferases (PRMT). Type I PRMT is responsible for the synthesis of ADMA. According to some recent studies, PRMT 5 and PRMT 7 type II methyltransferases may also synthesize small amounts of ADMA [28,29]. Recently, it has been shown that oxidized low-density protein (LDL) via up regulation of type I PRMT genes may increase generation of ADMA [30]. However, it appears that ADMA accumulation in the state of renal dysfunction is a consequence of increased proteolysis and decreased eliminatory pathways. In addition to an extensive catabolism of proteins in the body, inflammation and oxidative stress may decrease DDAH activity (enzyme responsible for ADMA degradation). More specifically, oxidative stress, which is strongly present in manifestations of ESRD, my affect DDAH activity by modification of a critical cysteine residue in the enzyme's active site [31]. Also, reduced DDAH activity might be due to an effect of different stimuli such as inflammatory cytokines, hyperhomocystinemia, hyperglycemia, and infectious agents [32-35].

With regards to SDMA, it has been demonstrated that it is a strong determinant of both GFR and the extent of coronary atherosclerosis in patients with ischemic heart disease and mild to moderate chronic kidney disease [16]. The fact that renal function is an important determinant for SDMA concentrations is not new, since urinary excretion is generally accepted as a SDMA modulating process. In our study, SDMA failed to predict mortality, its correlation with the BMI indicated a substantial dependence of SDMA level upon protein proteolysis.

Several studies [36,37] have reported that CRP is independently associated with all-cause and CVD mortality, but its prediction power is two times weaker than that of IL-6. CRP inability to predict long-term mortality by multivariate Cox regression model was shown in a 10-year follow-up study [38]. This study reported close relationship between CRP and aortic wall calcification, and suggests that CRP may reflect the severity of atherosclerosis [38].

Mallamaci et al. [39] had examined prognostic value of combined use of ADMA, CRP and B-type natriuretic peptide (BNP) in patients with ESRD. According to their data, ADMA and CRP is the second combination for identifying patients with highest risk for death, whereas the highest prognostic value was shown by the combination of CRP and BNP.

The latest study from Tripepi et al. [40] showed that inflammation amplified the risk of all-cause mortality and cardiovascular mortality in association with high ADMA levels in this population. However, the prognostic values of ADMA and CRP from this study couldn't be compared with prognostic values from our own study due to the fact that different statistical methods have been applied. Results from this study indicate that inflammation and endothelial dysfunction are parallel processes in patients on dialysis.

From its development up until its routine use, clinical marker should be standardized and cost-effective. Main advantage of CRP as a marker is its routine clinical use, as opposed to ADMA whose application has not yet been standardized. On the other hand, CRP is a non-specific inflammation marker, often elevated in the number of clinical conditions such as infectious diseases, surgical interventions and injuries. The advantage that ADMA has over CRP is that it can exclude clinical inapparent acute infection. Yet nowadays, its routine application is still difficult since its reference values are not available. The advantage of SDMA as a potential marker is that it increases to 10-fold in patients with end-stage renal disease while ADMA increases up to twice, but our and other studies showed that SDMA is not a good predictor of mortality. Although, this study speaks in favor of ADMA standardization and everyday clinical use; further studies are needed to establish its causal effect.

There are possible limitations to our study. Firstly, all tested markers are measured only at a single timepoint. Hence, the baseline measurements have been associated with the all-cause and cardiovascular mortality in several studies. Also, based on serial measurements one study demonstrated that CRP levels were stable with minimal intrapersonal variation during several years [41]. Lastly, there were overall small numbers of events. The findings that ADMA predicts all-cause mortality in patients on dialysis does not prove causality.

In conclusion, our data shows that ADMA is an independent and a better marker of all-cause and cardiovascular mortality than CRP alone. SDMA, however, failed to predict death in this population. To determine contribution of each predictor, it is needed to convey many prospective interventional studies and standardization of ADMA assay. Effort to determine the best predictors must be constant and unfailing because the risk stratification is the only way to direct attention to the vulnerable population and their better management.

Conflict of interests

The authors declare they have no conflict of interests.

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