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ORIGINAL ARTICLE

Associations between plasma osteopontin, sex, and 2-year global and cardiorenal outcomes in older outpatients screened for CKD: a secondary analysis of the SCOPE study

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ABSTRACT

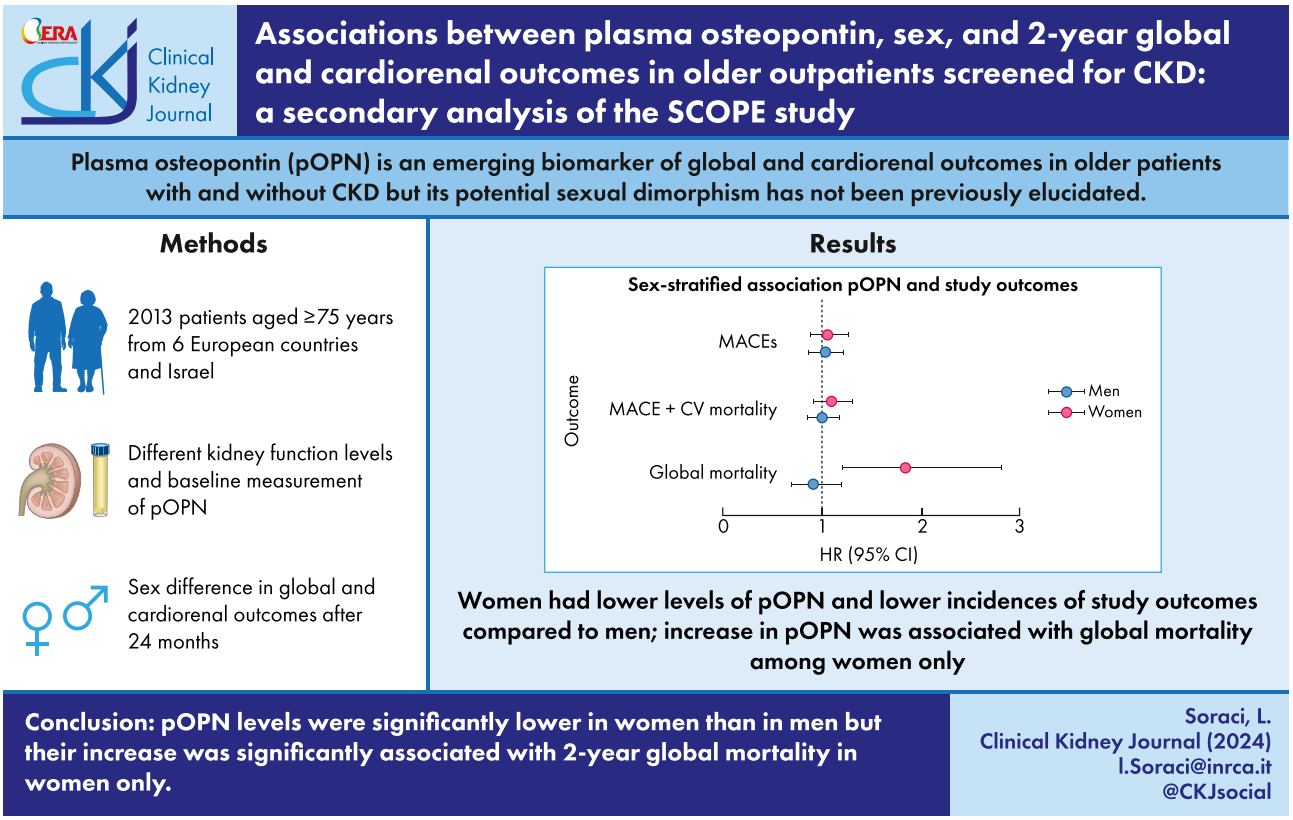
Background. Plasma osteopontin (pOPN) is a promising aging-related biomarker among individuals with and without kidney disease. The interaction between sex, pOPN levels, and global and cardiorenal outcomes among older individuals was not previously evaluated.

Methods. In this study we investigated the association of pOPN with 24-month global mortality, major cardiovascular events (MACEs), MACEs + cardiovascular (CV) mortality, and renal decline among older individuals; we also evaluated whether sex modified observed associations. pOPN levels were measured in a cohort of 2013 outpatients (908 men and 1105 women) aged 75 years or more enrolled in the context of a multicenter prospective cohort study in Europe. Multivariable linear regression, Cox and Fine Gray models, and linear mixed regression models were fitted to evaluate whether sex modified the associations between biomarkers and study outcomes.

Results. In total, 2013 older participants with a median age of 79 years, 54.9% of whom women, were included in the study; increased pOPN levels were associated with all-cause mortality specifically among women [reduced fully adjusted model resulting from backward selection, hazard ratio, 95% confidence interval (CI): 1.84, 1.20–2.89]. Addition of pOPN to models containing age, eGFR, and albumin-to-creatinine ratio (ACR) improved the time-dependent area under the curve (AUC) at 6, 12, and 24 months, among women only. No significant association was found between the biomarker levels, MACE, and MACE + CV mortality. Conversely, increased baseline pOPN was associated with eGFR decline in all patients (−0.45, 95%CI: −0.68 to −0.22 ml/min/1.73 m^2 year) but with slightly steeper declines in women compared to men (−0.57, −0.99 to −0.15 vs −0.47, −0.88 to −0.07).

Conclusions. pOPN levels were significantly lower in women than in men but associated with all-cause mortality in women only; increase in serum pOPN was associated with eGFR decline over time in all patients, but with stronger associations among women. Assessment of pOPN may help identifying older female participants at risk of poor outcomes.

GRAPHICAL ABSTRACT



Keywords: biomarkers, chronic kidney disease, older patients, osteopontin, renal decline

KEY LEARNING POINTS

What was known:

- pOPN is a matricellular glycoprotein involved in several biological activities and recently emerged as a biomarker of global and cardiovascular outcomes in patients with and without chronic kidney disease (CKD).
- pOPN levels were shown to increase in patients with CKD and were positively associated with other indicators of kidney damage and dysfunction.
- However, despite this relative abundance of data on the association of pOPN with global and cardiorenal outcomes in multiple cohorts, data in older populations are limited to men and did not address the potential effect modification of sex in the observed relationships.

This study adds:

- Increase in pOPN levels were associated with 2-year all-cause mortality specifically among older women screened for CKD.
- A multiplicative interaction between female sex and pOPN was found in models predicting all-cause mortality.
- Associations between pOPN and eGFR decline were present in all individuals, but slightly stronger among women.

Potential impact:

- Assessment of pOPN may help identifying older female participants at risk of poor outcomes and assist clinicians in tailoring targeted interventions.

INTRODUCTION

Plasma osteopontin (pOPN) is a matricellular glycoprotein involved in several biological activities because of its ubiquitous expression in the main human tissues and organs [1]. It primarily functions as a modulator of immune response and is involved in the control of local biomineralization, calcification signaling [2], and wound healing [3]. By interacting with integrin receptors and CD44, pOPN can activate signaling pathways that suppress bone mineralization; in vascular smooth cells, calcification-inducing signals, such as elevated serum phosphate levels, trigger the upregulation of pOPN thus preventing the progression of vascular calcification by decreasing deposition of calcium phosphate [2, 4]. pOPN is also upregulated during inflammatory processes that characterize wound healing; its interaction with fibroblast and endothelial receptors induce cell migration, extracellular matrix deposition, and neoangiogenesis that contribute to healing processes [1, 3].

Recently, deregulation of pOPN signaling has been associated with obesity, diabetes, kidney injury, urinary stones [5], cardiovascular disease, and cancer [1]. Furthermore, it was also reported that pOPN could be able to capture patients at risk of global [6–10] and cardiovascular (CV) mortality [6, 9, 11]; interestingly, pOPN was found to increase in patients with CV events, showing also correlations with traditional CV risk markers [8, 10–15].

pOPN levels were shown to increase in patients with chronic kidney disease (CKD) and were associated with other indicators of kidney damage and dysfunction [6, 7, 9, 15–17]. In this regard, increasing serum pOPN levels were found to be associated with estimated glomerular filtration rate (eGFR) decline in patients with CKD of the German Chronic Kidney Disease (GCKD) study [18], although inclusion of pOPN in prediction models did not improve prognostic accuracy compared to traditional markers of kidney function such as eGFR and albumin-to-creatinine ratio (ACR) [19]. However, despite this relative abundance of data on the association of pOPN with global and cardiorenal outcomes in multiple cohorts, data in older populations are limited to men [11] and did not address the potential effect modification of sex in the observed relationships.

Accordingly, the aims of the study were to (i) examine the association of pOPN, all-cause mortality, major cardiovascular events (MACEs), MACEs + cardiovascular (CV) mortality, and eGFR decline among older individuals; (ii) to explore whether sex can modify the observed associations and whether inclusion of pOPN in regression models affected discriminatory capacity in men and women compared to traditional markers of kidney function (eGFR, ACR).

MATERIALS AND METHODS

Data source and study design

The present study uses data from the Screening for Chronic Kidney Disease among Older People across Europe (SCOPE) study (European Grant Agreement no. 634 869). Methods of the SCOPE study have been described elsewhere [20]. Briefly, all participants aged 75 or more attending outpatient services at participating institutions from August 2016 to August 2018 were asked to participate. After signing a written informed consent, enrolled participants underwent a comprehensive geriatric assessment including demographic data, socioeconomic status, physical examination, comprehensive geriatric assessment, bioimpedance analysis for determination of body composition, diagnoses (clinical history and assessment of clinical documentation exhibited by participants and/or caregivers), quality of life, physical performance, overall comorbidity, and blood and urine sampling. Participants were followed up for 24 months as previously described [21]. The study protocol was approved by ethics committees at all participating institutions and complies with the Declaration of Helsinki and Good Clinical Practice Guidelines.

Sample selection

Overall, 2461 participants were initially enrolled in the study. Of them, 200 were excluded from this study because of incomplete baseline kidney function data, as were 239 participants with missing pOPN. Finally, nine participants were excluded because of missing follow-up data, thus leaving a final sample of 2013 participants to be included in the analysis.

Definition of exposure and covariates

The collection of clinical and biochemical characteristics has been described in detail elsewhere [20]. Venous blood samples for pOPN measurements were drawn at the baseline visit in the morning after an overnight fast and stored in −80°C pending analyses.

pOPN was measured by using a commercial sandwich ELISA (DY1433, R&D Systems, Minneapolis, MN, USA) according to the recommendations of the manufacturer. The measuring range of the assay is 62.5–4000 pg/ml and the samples were diluted with 10 mg/ml bovine serum albumin in phosphate buffered saline (0.15 M NaCl, 0.02 M Na_2HPO_4, pH 7.2) to ensure that the samples were within the measuring range and to reduce the matrix and pH variations between plasma and urine. The total coefficient of variation (CV) for the assay was ∼6%.

Venous blood and urine samples for measurement of traditional metabolites were collected at all in-person study visits (baseline, and 1-year and 2-year study visits). These samples were used to analyze multiple biomarkers, including creatinine, cholesterol, parathyroid hormone (PTH), vitamin D, calcium, and phosphate.

Baseline serum creatinine was measured by isotope dilution mass spectrometry traceable standard method, and eGFR was calculated by creatinine-based Berlin Initiative Study (BIS) equation, which was specifically developed in a population older than 70 years [22]. Urinary ACR was also measured and included in the analysis.

Outcomes

Outcomes of the present study were all-cause mortality, MACEs, the combined end-point MACEs and/or CV mortality, and eGFR decline.

For participants dying during the follow-up period, information about date, place, and cause of death were collected from death certificates provided by relatives or caregivers. City or town registers were consulted to retrieve information about death when neither relatives nor caregivers could be contacted. Information about CV deaths and MACE were collected in keeping with the definitions in the Standardized Definitions for End Point Events in Cardiovascular Trials. CV death included death resulting from acute myocardial infarction, sudden cardiac death, heart failure, stroke, CV procedures, CV hemorrhage, and other CV causes [23]. MACEs included: Myocardial Infarction, Hospitalization for Unstable Angina, Transient Ischemic Attack and Stroke, and Heart Failure Event [24].

Analytical approach

Baseline characteristics were reported using descriptive statistics in the overall study population and in both men and women separately. Continuous variables were expressed as median and interquartile range (IQR) or mean and standard deviation (SD) according to their distribution assessed through visual inspection and the Kolmogorov–Smirnov test. Categorical variables were presented as absolute and relative (%) frequencies. Supplementary analyses were made across tertiles of serum pOPN (T1, T2, and T3), to explore how increasing pOPN levels may affect the biochemical, clinical, and demographic profile of older individuals. Intergroup comparisons were evaluated by *t*-test, Mann–Whitney, one-way ANOVA, and Kruskal–Wallis tests for continuous variables, while the chi-squared test was used for categorical data.

Linear relationships between baseline serum pOPN and renal and bone biomarkers (eGFR, ACR, PTH, vitamin D, calcium, phosphate) among men and women included in the study were assessed by Spearman's rank correlation test.

Investigation of the association between pOPN and study outcomes was made by modeling pOPN as a continuous variable undergoing a logarithmic transformation to account for its right-skewed distribution.

Survival analysis

Global and cardiovascular study outcomes (all-cause mortality, MACEs, MACEs + CV mortality) were standardized per 1000 person-years and were presented descriptively in both men and women. The person-days of follow-up computed from the day of the first outpatient visit to death or the end of the study. Kaplan–Meier curves were used to visualize the cumulative survival probability over the 2-year follow-up period in men and women separately, and across tertiles of pOPN. The association between pOPN levels and overall mortality was performed by using Cox proportional hazards regression models. Multicollinearity was investigated using the variance inflation factor (a value >3 was considered index of multicollinearity). Fine and Gray competing risk-adjusted hazard models were used to explore the association between pOPN MACEs, and MACEs + CV mortality, with all-cause mortality treated as competing risk.

We used three different regression models to investigate such associations based on the progressive inclusion of covariates retrieved by literature review:

- Model A: adjusted for age and sex.
- Model B: model A + eGFR, ACR, smoking status, and waist-to-hip ratio (WHR).
- Model C: model B + comorbidities (congestive heart failure (CHF), coronary artery disease (CAD), diabetes, atrial fibrillation, anemia, osteoporosis, cancer, cerebrovascular disease], medications known to affect pOPN levels [ACE inhibitors (ACEi), angiotensin receptor blockers (ARBs), beta blockers, calcium channel blockers, lipid-lowering drugs, antiplatelets], and markers of bone metabolism (parathyroid hormone (PTH), calcium, phosphate, and vitamin D). ACR, PTH, and vitamin D were logarithmically transformed because of their skewed distribution.

Given the relatively low number of events for all-cause mortality, Cox regression models B and C investigating this outcome were further filtered by applying a backward step-down variable selection based on the Akaike information criterion (AIC) and statistical significance of study variables ($P < .05$). We then compared fully and parsimonious models by reporting information according to AIC. Furthermore, we investigated whether addition of pOPN to ACR and eGFR improved the discriminatory power of Cox regression models, as measured by time-dependent area under the curve (AUC) at 6, 12, and 24 months [25].

Analyses to investigate the association between pOPN and eGFR decline were conducted in a sub-cohort of 1534 patients by using linear mixed models with random intercepts and random slopes to model the patient-specific eGFR trajectories, imposing no restrictions on the covariance. Interaction terms with time were also included to model the effects on the eGFR slope. Results are reported as coefficients and *P* values.

The baseline coefficient (main effect) can be interpreted as association with mean eGFR levels and the slope coefficient

Table 1: General characteristics of the whole study population and of men and women separately.

	Study population (2013)	Men (908)	Women (1105)	P
Age, median (IQR)	79 (77–83)	79 (77–83)	79 (77–83)	.82
WHR, median (IQR)	0.93 (0.88–0.98)	0.98 (0.94–1.02)	0.89 (0.85–0.93)	<.001
Smoking, *n* (%)	876 (43.5)	565 (62.2)	311 (28.1)	<.001
Hypertension, *n* (%)	1544 (76.79)	700 (77.1)	844 (76.4)	.75
Cerebrovascular disease, *n* (%)	258 (12.9)	134 (14.8)	124 (11.2)	.022
CHF, *n* (%)	348 (17.3)	178 (19.6)	170 (15.4)	.015
Diabetes, *n* (%)	488 (24.2)	271 (29.8)	217 (19.6)	<.001
CAD, *n* (%)	268 (13.3)	164 (18.1)	104 (9.4)	<.001
Atrial fibrillation, *n* (%)	312 (15.5)	167 (18.4)	145 (13.1)	.001
Anemia, *n* (%)	404 (20.1)	235 (26.0)	169 (15.3)	<.001
Cancer, *n* (%)	353 (17.5)	192 (21.1)	161 (14.6)	<.001
Osteoporosis, *n* (%)	604 (30.0)	130 (14.3)	474 (42.9)	<.001
PTH (pg/ml), median (IQR)	58.0 (41.4–84.2)	61.1 (44.0–91.7)	56.2 (40.2–79.2)	<.001
Calcium (mg/dl), mean (SD)	9.4 (0.5)	9.4 (0.5)	9.5 (0.5)	<.001
Phosphate (mg/dl), mean (SD)	3.3 (0.6)	3.2 (0.6)	3.5 (0.5)	<.001
Vitamin D (ng/ml), median (IQR)	22.9 (14.8–31.0)	21.3 (14.1–28.7)	24.3 (15.5–32.8)	<.001
eGFR, ml/min/1.73 m^2, median (IQR)	54.7 (43.8–63.5)	52.5 (40.8–61.8)	56.5 (46.3–64.5)	<.001
eGFR, ml/min/1.73 m^2, *n* (%)				<.001
≥60	674 (33.5)	260 (28.6)	414 (37.5)	
45–59.9	788 (39.2)	341 (37.6)	447 (40.4)	
30–44.9	413 (20.5)	223 (24.6)	190 (17.2)	
<30	138 (6.8)	84 (9.2)	54 (4.9)	
ACR, mg/g, median (IQR)	11.5 (3.8–32.0)	13.2 (4.4–59.8)	10.2 (3.3–24.2)	<.001
ACR, mg/g, *n* (%)				<.001
<30	1482 (73.6)	594 (65.4)	888 (80.4)	
30–300	395 (19.6)	218 (24.0)	177 (16.0)	
≥300	136 (6.8)	96 (10.6)	40 (3.6)	
ACEi/ARBs, *n* (%)	1131 (56.1)	525 (57.8)	606 (54.8)	.19
Beta blockers, *n* (%)	811 (40.3)	364 (40.1)	557 (40.4)	.90
Lipid-lowering drugs, *n* (%)	906 (45.0)	453 (49.9)	453 (41.0)	<.001
Calcium antagonists, *n* (%)	507 (25.2)	238 (26.2)	269 (24.3)	.36
Antiplatelets, *n* (%)	744 (37.0)	382 (42.1)	362 (32.8)	<.001
Anticoagulants, *n* (%)	317 (15.7)	179 (19.7)	138 (12.5)	<.001
Biphosphonates and other antiresorptive drugs, *n* (%)	158 (7.8)	30 (3.3)	128 (11.6)	<.001
Vitamin D and analogues,*n* (%)	423 (21.1)	178 (19.6)	245 (22.2)	.176
pOPN, ng/ml, median (IQR)	38.9 (27.4–56.1)	43.2 (29.7–61.5)	36.5 (25.8–50.8)	<.001

(interaction effect) as association with the eGFR variation over time. We applied the AIC on a model containing pOPN and covariates to investigate the importance of predictors.

All analyses were conducted in all participants and in both men and women to assess whether the interaction between sex and pOPN could modify the observed associations. A sensitivity analysis for eGFR decline was conducted by using CKD-EPI equation instead of BIS equation to estimate eGFR. All statistical analyses carried out by R software v.4.6. All tests of statistical significance were two-tailed, and $P < .05$ was considered statistically significant.

RESULTS

Baseline characteristics of the study population

Overall, the 2013 participants included in the study were aged 79 (77–83) years, and 48.9% were men (Table 1). The median pOPN, eGFR, and ACR levels were 38.9 (27.4–57.1) pg/ml, 54.7 (43.8–63.5) ml/min/1.73 m^2, and 11.5 (33.8–32.0)mg/g, respectively.

The 448 participants excluded from the analysis because of missing baseline kidney function or pOPN were older, more frequently men, with a higher WHR and serum PTH levels than the included ones. Additionally, they had a higher prevalence of diabetes and anemia, than the included participants. Finally, eGFR and ACR did not significantly differ between excluded and included participants.

The clinical and demographic profile was significantly different between men and women (Table 1). Compared to men, women were less commonly smokers and had a lower WHR, ACR, and PTH, but a higher eGFR, vitamin D, calcium, and phosphate; HDL cholesterol; additionally, they had a lower prevalence of several comorbidities (CV diseases, anemia, cancer, and diabetes), a lower prescription of lipid-lowering drugs, antiplatelet, and anticoagulant medications; conversely, they had a higher prevalence of osteoporosis and a greater prescription of bisphosphonates and other antiresorptive drugs compared to men pOPN levels were significantly lower in women compared to men.

Characteristics of the study population after stratification by pOPN tertiles are reported in Supplementary Material 1, Supplementary Table S1 Participants in the higher pOPN tertile were older, more commonly men, and smokers, with a higher prevalence of cardiovascular diseases, diabetes, anemia, and osteoporosis; they were also characterized by higher median levels of PTH and ACR, and by a lower eGFR, compared with other tertiles. Prescription of beta blockers, calcium antagonists, anticoagulants, and vitamin D and analogues increased with

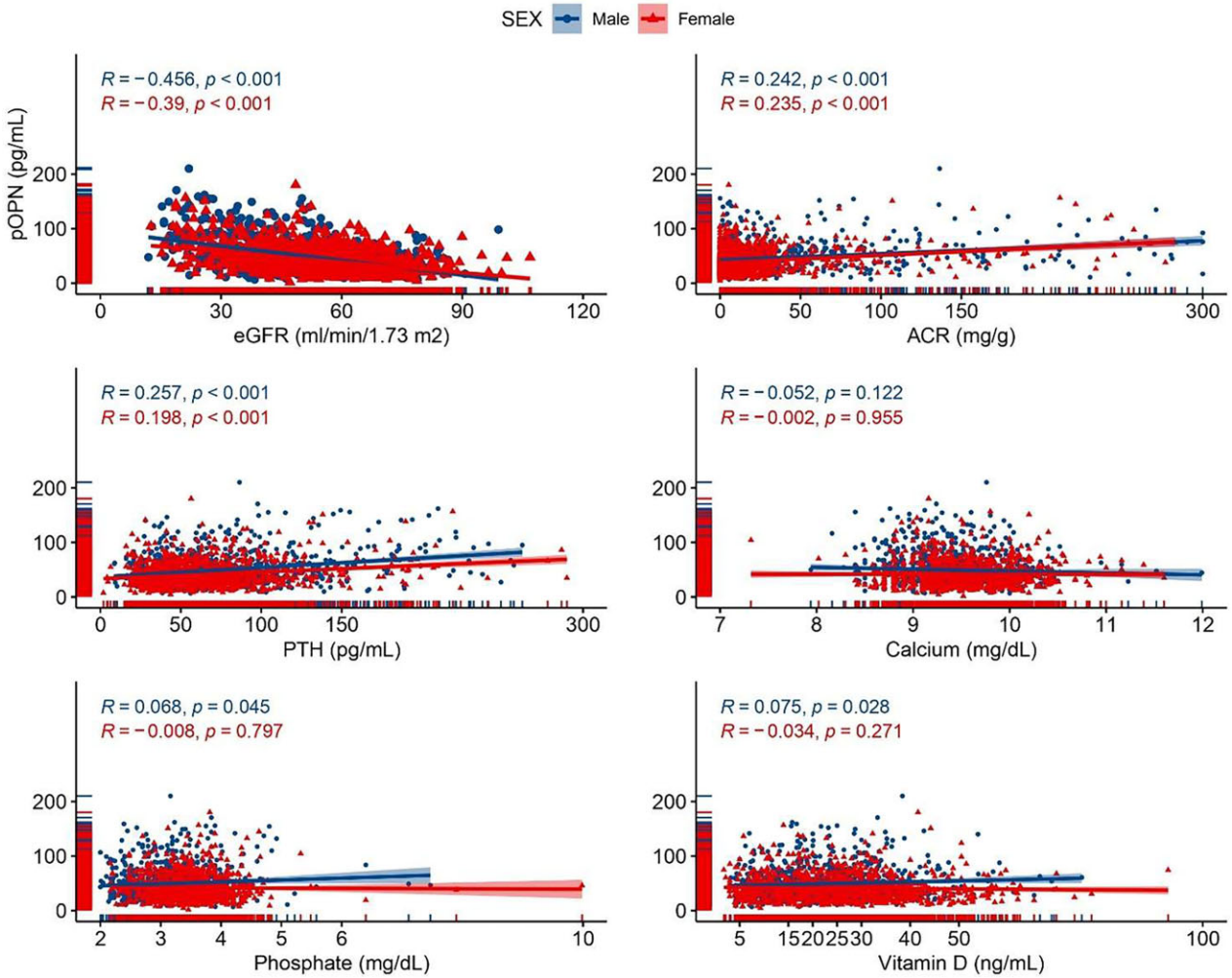


Figure 1: Correlations between pOPN, eGFR, ACR, PTH, calcium, phosphate, and vitamin D, in the overall study population and in men and women separately.

increasing pOPN tertiles. Conversely, prescription of bisphosphonates and other antiresorptive drugs progressively decreased with increasing pOPN tertiles.

Cross-sectional associations between pOPN and other biomarkers are shown in Fig. 1. pOPN was positively associated with ACR and PTH and negatively associated with eGFR in both sexes; a mild positive correlation between pOPN and both phosphate and vitamin D emerged only in men.

Association between pOPN and study outcomes

During a median follow-up time of 23 [22–24] months, 97 (4.8%) participants died, with an incidence rate (95%CI) of 25.7 per 1000 person-years; the corresponding figures for the other outcomes were: 322 (16.6%) and 97.5 per 1000 person-years for MACEs; 360 (17.9%) and 106.8 per 1000 person-years for MACE + CV mortality; −1.16 (−1.34, −0.98) ml/min/1.73 m^2 for eGFR decline rate per year. Overall, outcome incidence rates were significantly lower in women than in men for overall mortality ($P < .001$) and MACE + CV mortality ($P = .02$), while no significant difference was found for the incidence of MACEs only and eGFR decline (Table 2). In Cox proportional hazard models, pOPN was associated with global mortality in the whole study population, while associations with MACEs and MACE + CV mortality were non-statistically significant (Tables 3 and 4); in sex-stratified analyses, pOPN was strongly associated with global mortality only among women and a multiplicative interaction between sex and pOPN was detected ($P < .001$); furthermore, only among women the inclusion of pOPN in survival models investigating global mortality significantly improved the discrimination compared to models including eGFR and ACR only; indeed, time-dependent AUCs at 6, 12, and 24 months were 0.58, 0.68, and 0.77 for models including eGFR, ACR, and age; the corresponding figures for models including also pOPN were 0.68, 0.74, 0.81 ($P < .05$). By contrast, associations between pOPN, MACEs, and MACE + CV mortality were not statistically significant both in whole study population and sex-stratified analyses (Table 4). As regards the investigation of renal outcomes, pOPN was found to be associated with eGFR decline in all patients and in both men and women, but with stronger associations among women (Table 4).

DISCUSSION

Our analysis shows that higher levels of pOPN are associated with increasing severity of CKD stages in a population of older community-dwelling individuals; even though women had

Table 2: Incidence of study outcomes in the whole study population and in men and women separately.

Outcome	All (2013)	Men (908)	Women (1105)	P
Overall mortality per 1000 py (95%CI)	25.7 (20.6–30.8)	38.0 (28.7–47.3)	15.9 (10.4–21.3)	<.001
Overall mortality rate, *n* (%)	97 (4.8)	74 (7.0)	33 (3.0)	<.001
MACEs, per 1000 py (95%CI)	97.5 (86.8–108.1)	108.2 (91.4–125.0)	88.8 (75.1–102.5)	.21
MACEs, *n* (%)	322 (16.6)	160 (18.1)	162 (15.2)	.10
MACEs + CV mortality, per 1000 py (95%CI)	106.8 (95.8–117.8)	121.6 (104.0–139.2)	94.9 (80.9–108.9)	.02
MACEs + CV mortality, *n* (%)	360 (17.9)	183 (20.1)	177 (16.0)	.02
eGFR decline (ml/min/year), mean (95%CI)	−1.16 (−1.34, −0.98)	−1.18 (−1.44, −0.92)	−1.14 (−1.75, −0.53)	.41

py, person-years.

Table 3: Detailed comparison of full and reduced Cox regression models investigating the association between pOPN and all-cause mortality in the whole study population and among men and women as separate.

	Study population		Men	Women
Model B	Full model (AIC 1322.7)	Reduced model (AIC 1319.7)	Reduced model (AIC 768.4)	Reduced model (AIC 423.8)
pOPN	1.11 (0.89–1.39)	1.13 (0.91–1.42)	0.89 (0.67–1.18)	1.81 (1.19–2.77)*
Age	1.08 (1.03–1.13)*	1.09 (1.04–1.13)	1.11 (1.06–1.17)*	1.05 (0.97–1.12)
Female sex	0.54 (0.32–0.93)*	0.60 (0.39–0.92)		
eGFR	0.96 (0.95–0.98)*	0.96 (0.95–0.98)	0.97 (0.94–0.99)*	0.96 (0.94–0.99)*
ACR	1.28 (1.13–1.44)*	1.28 (1.13–1.44)	1.40 (1.20–1.63)*	1.13 (0.92–1.38)
Smoking status	1.15 (0.74–1.78)			
WHR	0.88 (0.66–1.18)			
Full model C	Full model (AIC 1333.7)	Reduced model (AIC 1309.0)	Reduced model (AIC 765.6)	Reduced model (AIC 418.5)
pOPN	1.23 (0.94–1.60)	1.15 (0.92–1.43)*	0.91 (0.69–1.20)	1.84 (1.20–2.80)*
Age	1.09 (1.04–1.14)*	1.08 (1.04–1.13)*	1.11 (1.06–1.17)*	1.05 (0.97–1.12)
Female sex	0.50 (0.28–0.91)*	0.50 (0.31–0.79)*		
eGFR	0.98 (0.96–0.99)*	0.97 (0.95–0.99)*	0.97 (0.95–0.99)*	0.97 (0.94–0.99)*
ACR	1.22 (1.07–1.41)	1.28 (1.13–1.43)*	1.39 (1.19–1.62)*	1.12 (0.91–1.38)
Smoking status	1.12 (0.70–1.78)			
WHR	0.91 (0.66–1.24)			
CAD	0.83 (0.44–1.57)			
Atrial fibrillation	0.55 (0.26–1.15)			
CHF	1.38 (0.79–2.38)			
Diabetes	1.14 (0.68–1.90)			
Anemia	1.38 (0.83–2.28)			
Osteoporosis	1.07 (0.61–1.87)	1.27 (0.81–1.99)		
Cancer	1.43 (0.87–2.33)			
CVD	0.64 (0.30–1.36)			
Lipid-lowering drugs	0.90 (0.54–1.50)			
Beta blockers	1.09 (0.68–1.77)			
Calcium channel blockers	1.12 (0.69–1.82)			
Antiplatelets	0.56 (0.32–0.99)*	0.63 (0.39–0.99)*		
ACEi/ARBs	1.01 (0.64–1.60)			
Biphosphonates and other antiresorptives	1.12 (0.43–2.92)			
Vitamin D and analogues	0.68 (0.38–1.20)			
Anticoagulants	2.09 (1.06–4.13)*	1.44 (0.91–2.28)		
PTH	0.87 (0.59–1.30)			
Calcium	1.02 (0.69–1.52)			
Phosphate	1.49 (1.13–1.96)*	1.47 (1.14–1.99)*	1.39 (1.01–1.90)*	1.53 (1.00–2.35)*
Vitamin D	1.17 (0.78–1.76)			

*P < .001

lower median pOPN levels and lower all-cause and CV mortality rates, associations between pOPN levels and globalmortality in fully adjusted models was significant only among women. Associations between biomarker levels, MACEs, and MACEs + CV mortality were not significant Finally, increase in pOPN levels was associated with accelerated eGFR in all individuals, but with stronger associations among women.

Previous studies have explored the prognostic role of pOPN in participants with and without CKD [6–8, 10, 11]. In this regard, participants with moderate to severe CKD were shown

Table 4: Investigation of the associations between Ln pOPN and study outcomes other than all-cause mortality in the whole population and in men and women separately.

	All	Men	Women
		MACE (HR, 95%CI)	
Model A	1.15 (1.02–1.28)	1.19 (1.03–1.39)	1.09 (0.92–1.28)
Model B	1.00 (0.89–1.13)	1.00 (0.85–1.20)	1.01 (0.85–1.20)
Model C	1.04 (0.92–1.18)	1.03 (0.86–1.22)	1.05 (0.88–1.27)
		MACE + CV mortality (HR, 95%CI)	
Model A	1.20 (1.08–1.34)	1.20 (1.04–1.38)	1.20 (1.03–1.41)
Model B	1.01 (0.90–1.13)	0.96 (0.82–1.12)	1.06 (0.89–1.26)
Model C	1.04 (0.92–1.17)	1.00 (0.85–1.18)	1.09 (0.91–1.30)
		CHF (HR, 95%CI)	
Model A	1.64 (1.28–2.18)	1.56 (1.07–2.29)	1.78 (1.15–2.72)
Model B	1.19 (0.88–1.62)	1.08 (0.70–1.67)	1.86 (0.87–2.13)
Model C	1.23 (0.90–1.68)	1.15 (0.74–1.80)	1.36 (0.86–2.14)
		BIS eGFR decline rate per year (LMM coefficient)	
Model A	−4.89 (−5.54, −4.23)*	−5.32 (−6.29, −4.35)*	−4.50 (−5.40, −3.62)*
Model B	−0.46 (−0.68, −0.25)*	−0.35 (−0.64, −0.06)**	−0.56 (−0.86, −0.25)*
Model C	−0.45 (−0.68, −0.22)*	−0.37 (−0.67, −0.07)**	−0.47 (−0.80, −0.14)**
		CKD−EPI eGFR decline rate per year (LMM coefficient)	
Model A	−6.89 (−7.78, −5.99)*	−7.63 (−8.98, −6.27)**	−6.22 (−7.41, −5.03)*
Model B	−0.57 (−0.85, −0.30)*	−0.45 (−0.84, −0.07)**	−0.67 (−1.06, −0.28)*
Model C	−0.56 (−0.86, −0.27)*	−0.47 (−0.88, −0.07)**	−0.57 (−0.99, −0.15)**

HR = hazard ratio.
*$P < .001$; **$P < .05$.

to have higher serum pOPN levels than healthy volunteers [9]; similarly, many studies demonstrated a linear increase of pOPN levels with declining renal function in both adult and elderly participants with CKD [6, 7, 11]. Furthermore, the physiological roles of pOPN may explain differences found in their association with kidney function in CKD. Indeed, pOPN is constitutively expressed by many organs, such as bone and kidneys [26]; pOPN upregulation characterizes several systemic dysfunctions, e.g. atherosclerotic plaque formation, development of insulin resistance, and deterioration of chronic inflammatory conditions [1, 27], diabetes and cardiovascular conditions, and both acute and chronic kidney diseases. Indeed, pOPN may play a central role in fostering chronic low-grade inflammation that characterizes moderate to advanced CKD and may contribute to eGFR decline and CKD progression [28]. To confirm this hypothesis, pOPN deficiency was found to be protective against aldosterone-mediated inflammation [29], while the use of anti-aldosterone drugs was found to decrease pOPN levels in previous studies [30].

As regards the relationship between pOPN with long-term mortality, several studies have shown a strong association between plasma OPN levels and all-cause mortality in participants with several conditions, such as chronic heart failure, septic shock, type 1 diabetes, acute kidney injury, and CKD [8–10, 31, 32]. However, most of the previous studies were conducted in selected groups composed of only adult participants (45–65 years old) and the only study that included older participants, had no female participants. In our cohort, a strong sexual dimorphism emerged in all analyses, suggesting the existence of sex-specific factors that may account for this variable risk.

In this regard, sexual hormones like estrogen and testosterone may affect OPN expression [33]; indeed, OPN gene promoter can be stimulated through estrogen-related response elements by estrogen-related receptor alpha (ERRα), as well as by estrogen receptor alpha (ERα) [34]. Therefore, the observed low circulating levels of OPN among older women in our study may at least be partly related to the blunted estrogen stimulation. However, clinical evidence is conflicting. In fact, a previous study showed no difference in pOPN levels among men and women with systemic lupus erythematosus [35], while another one highlighted that pOPN may increase in post-menopausal women [36]. Nevertheless, plasma OPN levels were found to be significantly lower among women compared to men in a population of 925 healthy adults [37], and our findings seems to be in keeping with this view. Interestingly, increase in pOPN was associated with global mortality only among women of our cohort, underlining for the first time the existence of a sex dimorphism of the association between pOPN and adverse outcomes in older individuals; furthermore, clinical significance of this finding is corroborated by the improvement of discriminatory ability of models including pOPN along with eGFR, ACR, and age, specifically among women, meaning that this biomarker can then improve detection of individuals at risk of poor outcomes. pOPN is able to promote tissue fibrosis, inflammatory cascades, and atherosclerotic plaque formation [38, 39], which are all down-regulated by estrogens [40–42], which may account for the lower global mortality of older women compared with men; however, as kidneys are involved in metabolizing and excreting estrogens, the presence of renal dysfunction can exacerbate the hormonal deficiency particularly in older women, who are exposed to lower estrogen concentrations compared to younger ones. Progressive estrogen deficiency can lead to increased phosphate retention and enhanced fibroblast growth factor 23 (FGF-23) production [43], which are markers of advanced CKD and substantially contribute to its poor outcomes by inducing vascular dysfunction, left ventricle hypertrophy, systemic and local inflammation, and muscle wasting [44]. FGF23 is secreted to contrast phosphate retention, but when eGFR declines, this hormone fails to maintain phosphate homeostasis thus leading to hyperphosphatemia despite abnormally high FGF23 levels;

hyperphosphatemia may stimulate pOPN synthesis and further lead to renal fibrosis and increased risk of death [45].

Increase in pOPN in older women may trigger activation of other estrogen-related or independent pathways. In this regard, pOPN was found to interact with some biomarkers of adipose tissue (e.g. leptin, and adiponectin) [46–48], which also have shown sexual dimorphism [49–51]. Similar considerations may support the finding of the association between pOPN levels and eGFR decline in overall study population but with higher strength in women; recent evidence has already shown that pOPN levels may help intercept the progression of CKD and the onset of kidney failure in patients with altered kidney function [18], but differences between men and women were not reported; the variation in pOPN levels between males and females, as well as the potential existence of a sex-related dimorphism and its underlying pathways, require further investigation.

Finally, our finding of nonsignificant associations between pOPN and MACEs may be due to the older age of study participants and shorter follow-up period of this study compared with the previous ones reporting this association; furthermore, previous studies were conducted on populations with higher cardiovascular risks, including patients with peripheral artery disease [52], and chronic stable angina [12]; these populations are characterized by an increased risk of adverse cardiovascular events and who may be exposed to chronic and higher elevations of pOPN with subsequent different effects on cardiovascular events. The absence of serial measurements of pOPN levels did not allow us to address this issue.

Our findings should be interpreted with the following limitations. First, the observational study design may have generated confounding by indication. Second, the absence of serial measurements of biomarker levels did not allow us to assess the temporal relationship between biomarker trajectories over time and study outcomes. Third, we cannot rule out the effect of residual confounding due to unmeasured biological variables regulating the expression of pOPN, such as alkaline phosphatase, leptin, and FGF 23; moreover, the length of the follow-up might be too short to intercept the association between pOPN and cardiovascular outcomes. This is confirmed by the observation of a nonstatistical trend of positive association between this biomarker and incidence of heart failure during the 2-year follow-up. Finally, survival bias could have led to a ceiling effect in which individuals with the most unfavorable profiles were not included or could not be followed up. However, our study has also several strengths. First, we included a real-world large population of older outpatients enrolled by using a limited set of inclusion/exclusion criteria; as such, our findings may be relevant to a broad population of older adults across Europe; second, this is the first study to show the effect modification by sex in the association between pOPN and outcomes in a population of older individuals. Future research with longer follow-up periods and comprehensive biomarker assessments is essential to validate our results and further elucidate the underlying mechanisms at play.

CONCLUSION

Women had a lower incidence of total mortality and MACEs + CV mortality compared to men. pOPN levels were significantly lower in women than in men but their increase was significantly associated with 2-year global mortality in women only; furthermore, increase in serum pOPN was associated with eGFR decline over time in all patients, but with stronger associations among women. Assessment of pOPN may help identifying older female participants at risk of poor outcomes and assist clinicians in tailoring targeted interventions.

SUPPLEMENTARY DATA

Supplementary data are available at *Clinical Kidney Journal* online.

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AUTHORS' CONTRIBUTIONS

L.S. performed statistical analysis, literature search, and manuscript drafting and revision. F.L. conceived the study, coordinated study protocol and data collection, and participated in manuscript drafting and revision. J.Ä., A.C.C., T.R.F., and A.L. performed laboratory assessment of plasma and urinary osteopontin, and participated in study protocol design, data collection, and manuscript revision; B.S., J.K., L.M., and S.M. participated in literature search and manuscript revision; R.R.W., G.W., F.M.R., L.T., F.F., R.M.G., R.A.M., I.M., C.W., and C.S. participated in study protocol design, data collection, and manuscript revision. All authors have read and agreed to the published version of the manuscript.

INFORMED CONSENT STATEMENT

Informed consent was obtained from all participants prior to their inclusion in the study.

INSTITUTIONAL REVIEW BOARD STATEMENT

The study was conducted in accordance with the Declaration of Helsinki, and approved by ethics committees in participating institutions as follows: Italian National Research Center on Aging (INRCA), Italy, #2015 0522 IN, 27 January 2016; University of Lodz, Poland, #RNN/314/15/KE, 17 November 2015; Medizinische Universität Graz, Austria, #28–314 ex 15/16, 5 August 2016; Erasmus MC University Medical Center Rotterdam, The Netherlands, #MEC-2016-036 #NL56039.078.15, v.4, 7 March 2016; Hospital Clínico San Carlos, Madrid, Spain, #15/532-E_BC, 16 September 2016; Bellvitge University Hospital Barcelona, Spain, #PR204/15, 29 January 2016; Friedrich Alexander University Erlangen-Nu¨rnberg, Germany, #340_15B, 21 January 2016; and Helsinki committee in Maccabi Healthcare services, Bait Balev, Bat Yam, Israel, #45/2016, 24 July 2016.

DATA AVAILABILITY STATEMENT

Data will be available for the SCOPE consortium on request from the principal investigator, Fabrizia Lattanzio, Italian National Research Center on Aging (IRCCS INRCA), Ancona, Fermo, and Cosenza, Italy. f.lattanzio@inrca.it.

CONFLICT OF INTEREST STATEMENT

The authors declare they have no conflict of interest. The funding body had no role in the design of the study and collection, analysis, and interpretation of data, writing the manuscript and in the decision to publish the results.

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