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ORIGINAL ARTICLE

Association between advanced oxidation protein products and 5-year mortality risk among amazon riparian elderly population

T. O. Silva[1]*, I. E. C. Jung[2]*, R. N. Moresco[5], F. Barbisan[2], E. E. Ribeiro[4], E. A. M. Ribeiro[4], K. Motta[4], E. Britto[4], E. Tasch[5], G. Bochi[5], M. M. F. Duarte[3], A. R. Oliveira[3], M. Marcon[3], C. Belló[3], G. F. dos Santos Montagner[3] & I. B. M. da Cruz[1,2,3]

[1]*Programa de Pós-Graduação em Bioquímica Toxicológica, Universidade Federal de Santa Maria, Brazil,* [2]*Programa de Pós-Graduação em Farmacologia, Universidade Federal de Santa Maria, Brazil,* [3]*Laboratory of Biogenomic, Universidade Federal de Santa Maria, Brazil,* [4]*Universidade Aberta da Terceira Idade, Universidade do Estado do Amazonas, Brazil, and* [5]*Programa de Pós-Graduação em Ciências Farmacêuticas, Universidade Federal de Santa Maria, Brazil*

Abstract

Proteins are important targets of several modifications caused by oxidative stress, leading to structural changes and consequently partial or total loss of their functions. The oxidized proteins include advanced oxidation protein products (AOPP) derived from oxidation-modified albumin, as well as fibrinogen and lipoproteins. An increase in AOPP levels indicates an oxidative stress state and the presence of coexisting inflammation. Several investigations have also suggested an association between high AOPP levels and aging-related diseases. However, the link between elevated AOPP levels and elderly mortality risk has not yet been investigated. Here, we report on a 5-year longitudinal study that investigated the potential association between AOPP levels and mortality using a population-based representative sample of riparian elders living in Brazilian Amazon region (Maués-AM). Age, sex, socioeconomic and cultural conditions, chronic morbidities, polypharmacy, and previous morbidities were also tested as potential confounders. The AOPP levels were measured in 540 (84.78%) individuals, all of whom were followed over a 5-year period in order to establish the mortality rate. Within this study period, 74 (13.7%) elders died and 466 (86.3%) survived. The AOPP levels were higher among the elders who died within the 5-year period (46.27 ± 40.6 mmol/L) compared with those who survived (36.79 ± 20.84 mmol/L) ($p = 0.002$). The analysis confirmed the link between high AOPP levels and mortality risk, independent of other intervenient factors. These results suggest that elevated AOPP levels could be used to predict mortality risk in elderly patients.

Keywords: advanced oxidation protein products, aging, epidemiology

Introduction

Many aging characteristics leading to dysfunction and chronic diseases are modulated by oxidative stress. This status is caused by imbalance between production and catalysis of reactive oxygen species, reactive nitrogen species, and other highly reactive mediators, such as advanced glycation end-products (AGEs) that attack macromolecules participating in body structure and function [1–3]. Proteins are important targets of several modifications caused by oxidative stress, such as oxidation, glycation, and conjugation with products of lipoperoxidation, leading to structural changes and consequently partial or total loss of function [1].

Among the oxidized proteins, advanced oxidation protein products (AOPP) derived from oxidation-modified albumin, as well as fibrinogen and lipoproteins, are of particular importance. AOPP are physiologically produced in small quantities during one's lifespan. They are being cleared from the organism by the liver and spleen, as a result of reaction between plasma proteins and chlorinate oxidants produced by myeloperoxidase [4,5] and potentially by Fenton reaction [6]. Increased AOPP levels indicate an oxidative stress state and coexisting inflammation, since these molecules trigger the oxidative burst and the synthesis of inflammatory cytokines in neutrophils and monocytes [7].

Several authors have described the association between high AOPP levels and uremia [8], nephropathies [9], coronary artery diseases, major adverse cardiac events [10–13], type 2 diabetes [14–16], metabolic syndrome (MS) [17], depression related to smoking habit [18], and some types of cancer: colorectal carcinoma [19,20] and breast cancer [21].

However, whether elevated AOPP levels could be associated with elderly mortality risk had not been investigated to date. Therefore, the major objective of this study is to test the association between AOPP levels and mortality. This research thus follows a 5-year longitudinal study design, using a population-based representative sample of riparian elders living in Brazilian Amazon region (Maués-AM). Age, sex, socioeconomic

*The two first authors contributed equally to development of the study.

Correspondence: Ivana B.M. da Cruz, Av Roraima 1000, Prédio 19, Santa Maria-RS, 97105900, Brazil. Tel/Fax: 55-55-32208163. E-mail: ibmcruz@hotmail.com

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and cultural conditions, chronic morbidities, polypharmacy, and previous morbidities were also tested as potential confounders.

This population was chosen because elderly individuals living in highly urbanized areas generally present several sociocultural, economic, and lifestyle differences. They have easy access to health services, and a multitude of other factors can influence the results obtained. In contrast, the riparian elderly population studied here is characterized by uniformity in terms of several sociocultural, economic, lifestyle (including dietary pattern), and other environmental aspects. Moreover, as they typically enjoy good health, all individuals included in this study exhibited high physical function at the start of the research period [22].

Materials and methods

Study population

This investigation focused on the riparian elders treated by Family Health Program (FHP), a public and free Brazilian health service. The study participants live in Maués-AM city, located in Amazon Rainforest Region, which is accessible by boat or plane only. This partial isolation limits the use of specialized health services and medical treatment available only in Manaus, which is the largest city of Amazonas State. The study commenced in 2009 and included all individuals in this region who were at least 60 years old at the time. The socioeconomic, cultural, health, lifestyle, fitness, and biochemical indicators of these subjects were previously evaluated and described in two cross-sectional studies [19,23]. Therefore, this is a complementary study that follows a longitudinal epidemiological design, aiming to evaluate the association between AOPP levels and mortality of riparian elders. This study is part of a project previously approved by the Ethical Committee of the University of the State of Amazonas. Since the vast majority of the elders included in this study were illiterate, oral consent or fingerprint was obtained to indicate their voluntary participation in the investigation, which was sought after the researchers read the consent form to the volunteers.

Data collection

The study population consisted of 637 individuals, who took part in the first phase of the study, conducted in July 2009. At this time, these people were also evaluated by a multidisciplinary research team, which included a physician, a nurse, a nutritionist, a psychologist, a physical educator, a physiotherapist, and several biologists. A structured interview was conducted to obtain the following data: demographic variables (education, income, marital status, and occupation), as well as lifestyle (smoking habit), central venous catheter (CVC) risk factors (hypertension, type 2 diabetes, obesity, dyslipidemia, and metabolic syndrome), history of previous chronic diseases (including CVC morbidities and hospitalization in the last year), and use and quantity of daily medication [19].

Anthropometric data collection, as well as functional and balance variables, were collected at this stage, following the methodology described by Kilic N et al. [20] and Avinash SS et al. [19]. The standard desk mercury sphygmomanometers (Wanross®) and stethoscopes (Littman®) were used to assess blood pressure (BP), which was measured at least 30 minutes after the last caffeine intake or cigaret smoked. Two measurements were taken with an initial rest of five minutes and subsequently at two-minute intervals, when an increased diastolic (DBP) or systolic blood pressure (SBP) was recorded.

To perform the biochemical analysis, peripheral blood was collected by venipuncture in the morning (20 mL), as well as after an overnight fast of at least 12 hours. Snacks and coffee were offered to the subjects following this procedure. The blood samples were collected in lithium heparin and ethylenediaminetetraacetic acid and were subsequently frozen and stored at −4ºC until needed for biochemical analyses. The following blood tests were performed: (1) glucose, total cholesterol, high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), and triglycerides (TG); (2) total cholesterol, HDL-c, TG, uric acid, and glucose (determined by enzymatic colorimetric methods using commercial kits); (3) total cholesterol Cod-Ana Labtest (Cat.76, Lagoa Santa, Brazil), HDL-c precipitant Labtest (Cat.13, Lagoa Santa, Brazil), TG Gpo-Ana, Glucose PAP Labtest (Lagoa Santa, Brazil), and LDL-c (calculated according to the Friedewald equation: (LDL-c) = (TG) − (HDL-c + TG/5)). Estimates of lipid peroxidation were quantified by spectrophotometric measure of formation of thiobarbituric-acid-reactive substances (TBARS) [24].

The AOPP was measured using a Cobas Mira Plus clinical chemistry analyzer, applying the technique described by Semba et al. [25]. The AOPP levels determined at this stage were used to establish whether this variable could influence the mortality of the riparian elders during the 5-year period included in this study.

Data mortality record collection

A 5-year prospective follow-up was performed to evaluate the survival rate in the study population. Official death records (dates and specific causes of death) for all deceased participants were obtained in Municipal Health Department of Maués City registration. The deaths were computed monthly, with the maximum survival period of 60 months (duration of the study), and the minimum of one month following the commencement of the study.

Statistical analyses

All statistical analyses were performed using the SPSS/PC statistical package, version 19.0 (SPSS Inc.,Chicago, IL, USA). The potential association between the AOPP levels and mortality during the 60-month follow-up was evaluated. To perform this analysis, the elders were initially

classified into three groups (lower, medium, and higher), according to the AOPP levels, as determined by percentile values distribution. The survival of elders with lower and higher AOPP levels (≥ 80 percentile) was compared by performing the survival analysis. Here, the Kaplan–Meier method was used, as this model is based on time and could follow the study participants over the 60-month study period, or until death. Potential effect of intervenient variables in the results obtained here (sex, age, chronic disease, polypharmacy, socioeconomic, cultural, lifestyle, and self-rated health) was determined by multivariate Cox proportional hazards method (backward Wald). All variables are presented as mean ± SD (standard deviation) (for continuous variables) or number and percentage (for categorical variables). In all analyses, $p < 0.05$ was considered statistically significant.

Results

Of the 637 riparian elders included in the research in 2009, 540 (84.78%) were assessed for levels of AOPP and followed over a 5-year period in order to establish the mortality rate. The remaining 97 individuals were excluded from the analyses because of incomplete data that could compromise the results. Of the 540 elders who were followed during the subsequent 5-year period, 74 (13.7%) died and 466 (86.3%) survived. The AOPP levels were higher in the elders who died (46.27 ± 40.6 mmol/L) than in those that survived (36.79 ± 20.84 mmol/L) ($p = 0.002$). The possible influence of sex, age, daily medicine, and previous diagnosed morbidities on AOPP levels was also evaluated and was found not to affect the AOPP levels. Surprisingly, younger elders (≥ 60–69 years) also presented higher AOPP levels (47.33 ± 19.71 mmol/mL) than older subjects (33.21 ± 25.70 mmol/L) ($p = 0.0001$).

The AOPP percentile distribution of riparian elders categorized by age and survival (Figure 1) was used to form two groups, comprising elders with low (AOPP-L < 60 mmol/L) and high AOPP levels (AOPP-H ≥ 60 mmol/L). The Kaplan–Meier survival curve shown in Figure 2 confirmed the association between the AOPP levels and elderly survival ($p = 0.034$). The means and standard errors for survival time in elders with low AOPP levels (< 60 mmol/L) was 49.61 ± 0.46 months, while for those with high levels (≥ 60 mmol/L) it was 46.27 ± 1.70 months.

The characteristic baselines and health indicators of the elders in the AOPP-L and AOPP-H groups were compared and the main results are presented in Table I and Figure 3. As expected, individuals in the AOPP-H group presented higher lipoperoxidation estimated by TBARS, compared with those in the AOPP-L group. However, the AOPP-H group also presented significantly lower triglyceride concentration. Despite the significant association between AOPP and triglyceride concentrations, the latter did not show significant association with riparian elderly survival ($p = 0.393$).

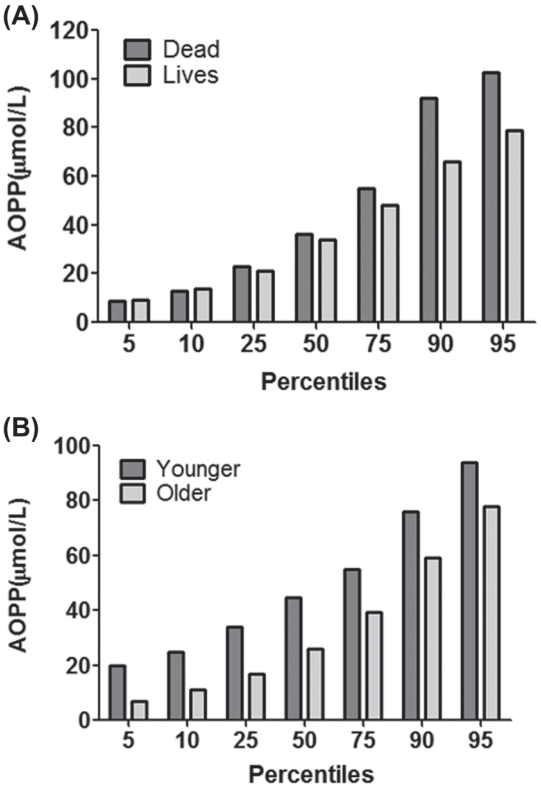

Figure 1. Percentiles distribution of AOPP levels between dead and living riverine elders (A) and between younger (60 < 70 years) and older (≥ 70 years) elders (B).

No association between AOPP polypharmacy and hospitalization in the last year was observed in the AOPP-H group. In relation to previous morbidities, we did not observe any association between AOPP levels and diseases, with exception of type 2 diabetes, which showed a tendency of association with elevated AOPP levels. However, the association between diabetes and AOPP-H was not significant. As smoking habit can be associated with high AOPP levels, the influence of this variable was also

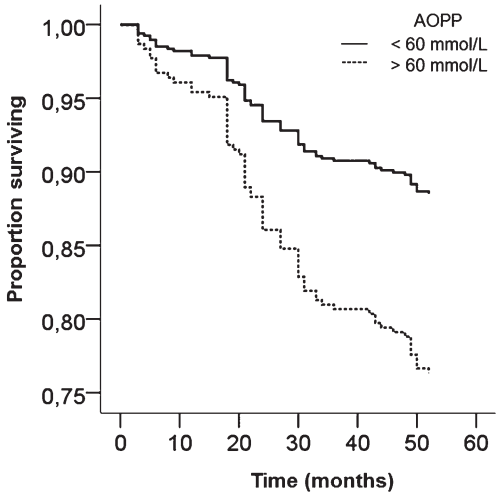

Figure 2. Kaplan–Meier survival curves for mortality of Amazon riverine elderly subjects with lower (< 60 mmol/L) and higher (> 60 mmol/L) AOPP.

Table I. Baseline characteristics among Amazonian riparian elderly with different advanced oxidative protein products (AOPP).

Variables	AOPP groups		
	< 60 µmol/L Mean ± SD	> 60 µmol/L Mean ± SD	*p*
Age (years)	72.7 ± 7.8	69.7 ± 7.6	0.003
BMI (Kg/m^2)	25.3 ± 4.9	25.8 ± 4.1	0.403
Waist circumference (cm)	88.1 ± 13.9	87.6 ± 16.9	0.769
SBP (mmHg)	129.0 ± 28.1	131.2 ± 20.1	0.543
DBP (mmHg)	72.9 ± 15.0	75.4 ± 10.5	0.090
Glucose (mg/dL)	120.9 ± 47.5	123.1 ± 40.9	0.718
Cholesterol total (mg/dL)	207.9 ± 52.9	206.6 ± 49.4	0.873
Triglycerides (mg/dL)	165.2 ± 98.4	138.5 ± 55.6	0.005
LDL-cholesterol (mg/dL)	142.0 ± 49.4	154.6 ± 48.5	0.097
HDL-cholesterol (mg/dL)	73.3 ± 16.7	71.0 ± 18.4	0.513
TBARS	21.0 ± 8.9	24.1 ± 11.9	0.011

SD = standard deviation; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure. The groups were statically compared by Student *t* test.

evaluated. The smoking habit prevalence in sample analyzed was 11.9% (64). However, the AOPP levels between smokers and non-smokers were similar between the dead and living elderly subjects.

Multivariate Cox regression analysis was performed to establish whether the association between AOPP-H and elderly mortality could be influenced by some biological or health indicators. The results presented in Table II showed that—after adjusting to sex, age, type 2 diabetes, smoking habit, hypertension, CVD, other previous morbidities, polypharmacy, and hospitalization in the last year—the association between high AOPP levels and mortality remained significant. Moreover, we estimated that riparian elders with higher AOPP levels were twice as likely to die during the 5-year follow-up period as were their counterparts with lower AOPP levels.

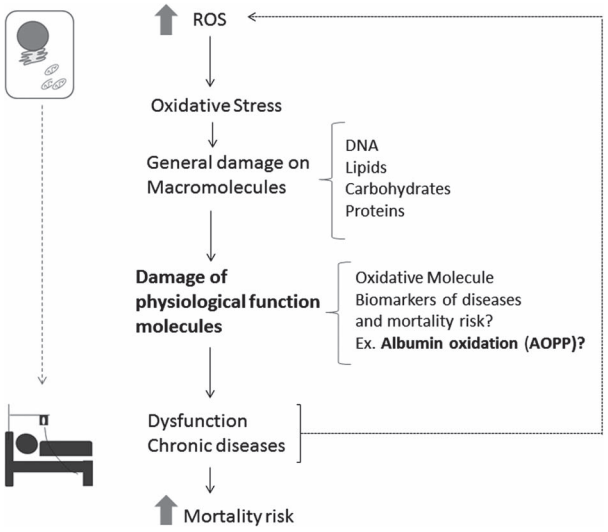

Figure 3. Comparison of chronic diseases prevalence in Amazon riverine elders categorized by lower (L = < 60 mmol/L) and higher (H = > 60 mmol/L) AOPP. The comparison was statistically performed using Student's *t*-test.

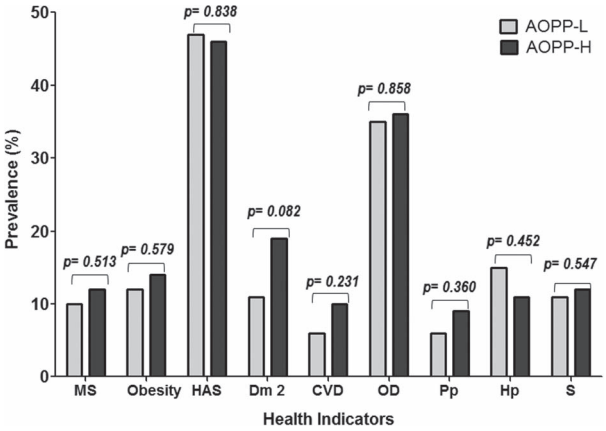

Figure 4. General model for explaining the potential relevance of AOPP as mortality biomarker in elderly subjects. The imbalance of oxidant and antioxidant molecules into the cells potentially causes oxidative stress by oxidation molecules such as DNA breakage, lipoperoxidation, and protein carbonylation. This condition increases the oxidation of some biological molecules such as albumin, increasing blood AOPP levels.

Considering that AOPP levels could be related to uncontrolled variables of metabolic diseases, such as hypertension, diabetes, and hypercholesterolemia, we performed a Pearson correlation analysis among AOPP and body mass index, waist circumference, SBP and DBP, glucose, cholesterol total, LDL-c, HDL-c, triglycerides, polypharmacy, and estimation of lipid peroxidation. The results of these analyses did not show any associations between AOPP levels and these variables; the only exception was TBARS, which was positively associated with this biomarker. However, the correlation was very low ($r^2 = 0.120$, $p = 0.006$).

Discussion

In the present study, we described a significant association between elevated AOPP levels and high mortality risk, based on a 5-year follow-up of a riparian elderly population. The extensive literature review conducted as a part

Table II. Multivariate Cox regression analysis to determine de influence biological and health indicator factors in the association between higher levels of advanced oxidized protein products (AOPPs) and 5-year riverine elderly mortality.

Variables	Wald	Risk	95% CI	*p*
AOPP (> 60 mmol/L)	5.818	2.122	1.243–3.937	0.007
Age	13.29	1.057	1.028–1.087	0.0001
Sex	0.123	1.103	0.684–1.724	0.725
Diabetes	0.262	1.216	0.574–2.576	0.609
Smoking habit	0.150	1.102	0.897–1.452	0.699
Hypertension	0.029	0.953	0.552–1.648	0.864
CVD	0.828	1.458	0.647–3.281	0.363
Other morbidities	0.002	1.10	0.617–1.656	0.967
Polypharmacy	1.763	0.861	0.90–1.074	0.184
Hospitalization in the last year	0.488	0.786	0.387–1.593	0.503

CVD = cardiovascular diseases;

of this study indicates that, to the best of our knowledge, this is the first attempt to describe the influence of AOPP levels on the elderly survival rates. However, several extant studies, including the investigation performed by Kregel et al. [26] suggested an association between high levels of serum protein carbonylation in moderate-to-severely disabled women (>65 years) and the 5-year mortality. The hazard ratio found by these authors after adjusting for confounder variables was 1.34 (CI95%:1.01–1.79). Although this hazard ratio is slightly smaller than that obtained in this work, it still corroborates the hypothesis that elevated protein oxidation levels could be an important biomarker of elderly mortality risk.

In fact, oxidative damage to proteins presents an important cascade effect in cell homeostasis, as it can lead to the loss of structural integrity and function [27]. Therefore, we consider that the results reported here have some biological plausibility, since albumin is the most abundant protein presenting pleiotropic effects. It plays a role in the transport of several molecules, including hormones and fatty acids, as well as in pH buffering and osmotic pressure maintenance. Generally, albumin is downregulated in inflammatory states and is an important biomarker of nutritional status [28]. Therefore, the oxidation of sulfhydryl groups (SH) in albumin can cause its depletion in blood, and this process can contribute to functional and structural disturbances [16]. For this reason, elevated AOPP levels can serve as a systemic oxidative marker of several chronic diseases and their complications. They can even be used to estimate mortality risk, as suggested by our data (Figure 4).

As previously noted, several prevalent diseases in elders have been associated with high AOPP levels, including cardiovascular disease (CVD), diabetes and subsequent complications, MS, and cancer [8–21]. Most studies attempting to establish the relationship between AOPP and various diseases followed case–control or cross-sectional design. However, literature review revealed some prospective studies describing the association between high AOPP levels and poor renal outcome of nephropathy [9], correlation with major adverse cardiac events during the 6-month follow-up period [12] and depressed smokers [18].

Our data showed an association between AOPP and 5-year mortality risk, independent of age, sex, medicine intake, and previous chronic diseases. Moreover, we failed to establish a correlation between AOPP levels and some biochemical and physiological markers of metabolic diseases. These results suggest that metabolic uncontrolled diseases are not the main cause of high AOPP levels and the subsequent mortality risk. Unfortunately, we did not measure renal and hepatic function biomarkers, as this could help us to elucidate the source of AOPP levels in the elders who died in the analyzed 5-year follow-up period.

On the other hand, as expected, the association between AOPP and age was inverse, whereby a greater number of younger subjects with higher AOPP levels died compared with their older counterparts. This result suggests that elevated AOPP levels (≥60 mmol/L) are not a characteristic associated with aging, but rather possibly represent a dysfunction or the presence of a disease (even if undiagnosed). Despite the uncontrolled increase in the protein carbonyl content, such as AGEs and AOPP—which are considered a hallmark of cellular and organismal aging—in most cases, the proteins targeted by these deleterious consequences have not yet been clearly identified [3,30]. An important question that emerges from results would impact antioxidant and antioxidant enzymes concentration in the blood on AOPP levels. However, in the presente study was not possible to analyze these variables in the investigation. Therefore, an additional investigation about the potential association between antioxidant levels and markers of AOPP study should be conducted. Thus, it is important to note that our study focused on a riparian population with limited access to health care and modern technologies. This provided us an opportunity to evaluate the impact of some oxidative biomarkers on survival of elderly people that are characterized by a reduced number of intervenient variables.

On the other hand, it is also important to point out some methodological constraints affecting the present study, such as lack of information about mortality causes. Unfortunately, the limited use of modern medical services by the studied population hindered establishing the cause of mortality in most cases. Another limitation is the low number of elders who died in the period analyzed, decreasing statistical power of the results. Thus, following of these elders for a longer period will help us elucidate if some previous dysfunction or morbidity that was not statistically associated with the deaths recorded in this study could contribute to the risk of mortality in this population. Other major limitation of our study is the difficulty of holding more complete diagnostics on the physiological status and health of the elders for logistical reasons. Maués is a place of difficult access because it is located in the Amazon rainforest. For this reason, the potential variables associated with high AOPP levels in this population need to be investigated from further studies.

However, we believe that these limitations did not invalidate the results reported here. Perhaps, similar investigations in other elderly populations, aiming to understand the role of AOPP in the participants' survival, could help expand our knowledge on this important issue.

Despite the limiting methodological factors of the study, based on our findings, we suggest that elevated AOPP levels can be used in predicting elderly mortality risk.

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Declaration of interest

The authors report no declarations of interest. The authors alone are responsible for the content and writing of the article.

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