Inflammaging: Analysis of a Risk Profile for Gerontocide by COVID-19 in Brazil

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Abstract

Introduction: The increase in inflammatory cytokines associated with a reduction in the bioavailability of zinc has been used as a marker for inflammation. Despite the high inflammatory state found in institutionalized elderly individuals, few studies have proposed verifying the factors associated with this condition in this population to pandemic COVID-19.

Objective: To verify the factors associated with inflamm-aging in institutionalized elderly.

Methodology: A total of 187 elderly individuals (≥ 60 years old) living in the nursing homes of Natal/RN were included in the study. After cluster analysis was used to identify 3 groups according to their inflammatory state, an analysis of sarcopenia and anthropometric, biochemical, sociodemographic and health-related variables was performed. In sequence, an ordinal logistic regression was performed for a confidence level of 95% in those variables with p <0.20 in the bivariate analysis.

Results: IL-6, TNFα and Zinc. Low-density lipids (LDL), high-density lipids (HDL) and triglycerides were associated with inflamm-aging. The increase of 1 unit of measurement of LDL, HDL and triglycerides increased the chance of inflammation-aging by 1.5%, 4.1% and 0.9%, respectively, while oldest old (≥80 years old) had 84.9% chance of presenting inflamm-aging in relation to no oldest old (<80 years).

Conclusion: The association between biochemical markers and inflamm-aging demonstrates a relationship between endothelial injury and the inflammatory state. In addition, the presence of a greater amount of fat in the blood may present a higher relative risk of death from COVID-19.

Introduction

The aging process occurs parallel to the progressive deterioration in cells and functioning of the organs due to metabolic, immunological, neuroendocrine, or oxidative stress [1,2]. These alterations during aging are explained by the imbalance between oxidant/antioxidant [2] and inflammatory/anti-inflammatory mechanisms resulting from the pro-inflammatory state known as *inflammaging* [3].

Inflamm-aging is a process that occurs concomitantly with aging and is related to the presence of a mild and chronic inflammatory state. A moderate inflammatory response is beneficial to the body, but when excessive, the response becomes harmful. For example, alterations are triggered by exacerbated

production of proinflammatory cytokines such as interleukin (IL-6), tumor necrosis factor alpha (TNFa), and interleukin 1β (IL-1β) [4,5].

In addition, the decline in zinc bioavailability is a process that occurs in aging parallel with exacerbation of the inflammatory state [6,7]. Zinc (Zn) deficiency in the elderly could result from a decrease in Zn intake, medication use, malabsorption syndromes or kidney diseases [8]. It is known that zinc has important roles in several physiological functions, such as in the oxidative stress cellular system, where it protects the cell from damage by free radicals; in blood clotting, it enhances the aggregation of circulating platelets; in insulin synthesis, secretion and signaling; bone homeostasis; and proper thyroid function; it acts as a neuromodulator in glutamatergic neurotransmission and is a relevant regulator of the innate and acquired immune system [8–12].

There is a growing body of literature suggesting that zinc plays a relevant role in the equilibrium of TH1/TH2 pathways of the acquired immune system by activating the anti-inflammatory “Signal Transducers and Activators of Transcription 3” (STAT3) pathway or by inhibiting the proinflammatory “Nuclear Factor kappa-light-chain-enhancer of activated B cells” (NF-κB) pathway. Therefore, shifting the immune response towards the proinflammatory Th2 system [9,13,14].

At physiological levels, zinc acts mainly by inhibiting the proinflammatory NF-κB pathway and consequently proinflammatory cytokines (IL-1, IL-6 and TNF-α) through several mechanisms and at many levels, for instance, upregulating A20 gene expression, increasing peroxisome proliferator-activated receptor alpha (PPAR-α) or inhibiting nucleotide phosphodiesterase (PDE) [14,15]. Moreover, as zinc deficiency is usually observed in aging, there is a hypothesis suggesting a close relationship between *inflammaging* and its deficiency [13].

Therefore, robust body evidence has shown that inflammation is present independent of whether elderly people are affected by diseases or are healthy [16]. It seems that inflammation is characteristic of successful and unsuccessful aging. However, inflammation has been linked with various diseases, such as Alzheimer's disease [17], Parkinson’s disease [18], cardiac disease [19], osteoporosis and insulin resistance [20], chronic respiratory disease [21] and cancer [22], where in some cases zinc deficiency has been associated [23].

In addition, it seems that inflammation is related to high mortality rates [24], especially in institutionalized elderly individuals who have an even higher rate [25]. This is possible because the institutionalized elderly present worse health status indicators, with a high prevalence of high inflammatory stress. Currently, these worries have expanded due to the COVID-19 Pandemic. The patients most affected by COVID-19 have shown comorbidities such as hypertension [26], diabetes [27], and kidney disease [28] and very high levels of systemic inflammatory biomarkers [29,30]. For this reason, they have more comorbidities and inflammation, and older age presents more risk factors associated with COVID-19 deaths [31,32].

Although a relationship has been established between inflammatory cytokine elevation and zinc reduction, with the onset of inflamm-aging, studies that explore this condition through the association of these markers are still scarce, especially in institutionalized elderly, probably due the high price of biomarker tests. However, it is extremely important to assess the factors associated with inflammation so that we can more easily trace the risk profile of these institutionalized elderly people and thus think more easily about protection strategies for this population, mainly during COVID-19 when the main conduct to avoid infection is social isolation, which is an impossible management in institutionalized elderly people.

Thus, the objective of the present study was to analyze the inflamm-aging profile in institutionalized elderly to warn of the need to protect this population, avoiding an even greater genocide due to the COVID-19 pandemic.

Methods

Study design and population

The study was conducted in 304 elderly people (≥ 60 years old) of both sexes, living in long-term care institutions for the elderly (LSIE) for or not for profit and registered in the Health Surveillance Agency (ANVISA), Brazil. The following individuals were excluded from the initial sample: elderly individuals who did not reside in LSIEs at the beginning of the collections, who presented difficulty in obtaining venous access, preventing blood collection to characterize the inflammatory state and biochemical variables (n=95). The project was approved by the Ethics and Research Committee of the Federal University of Rio Grande do Norte (CEP/UFRN), protocol 263/11; CAAE 0290.0.051.000-11. All experiments were performed in accordance with relevant guidelines and regulations. After explaining the methodological procedures and objectives of the study, all participants signed the Informed Consent Term prior to the beginning of the data collection.

Biomakers, anthropometric and sociodemographic variables and health-related factors.

Biomarker analyses

Blood was collected by venipuncture after a 12-14 hour overnight fast period. Lipid profile analyses were performed by the colorimetric method [33] (Labtest Diagnóstica® kits). Tumor necrosis factor (TNF) alpha and interleukin 6 (IL-6) were analyzed by chemiluminescence (Immulite 1000® and Siemens® kits). To minimize mineral contamination, all glassware and plastic containers used during the blood collection and zinc analysis were carefully demineralized in a 20% nitric acid bath for at least 12 h and rinsed 10 times with ultra-pure water [34] (*Direct-Q*® 3 Water Purification Systems, Merck Millipore, Darmstadt, Germany).

Anthropometric evaluation

From the anthropometric evaluation, the body mass index, calf circumference, muscle area of the arm (AMB), and fat area of the area (AGB) were calculated. The ratio of body weight (kg) to height (m) squared was used to calculate BMI [35]. The perimeter of the arm and tricipital skinfold, both measured at the midpoint between the acromion and olecranon of the ulna, were used to calculate the AMB and AGB from the equation proposed by Frisancho [36].

Sociodemographic variables

Data on sex, age, type of institution, and number of drugs and morbidities were obtained from the records of the participants at each institution. The variable "type of institution" was selected as a *proxy* for the economic situation of the elderly, considering the hypothesis that the current health status of the elderly reflects their past social and economic conditions. These conditions may determine the choice of the type of institution, whether for profit or not.

STATISTICAL ANALYSIS

To group the subjects according to the inflammatory state, some criteria were defined to analyze the variables to be grouped, followed by the analysis of the absence of multicollinearity between the variables that served as the basis for the construction of the *clusters*, from the Pearson correlation coefficient. Next, standardization of the variables was performed, transforming the data into Z-scores to standardize and prevent distortion of the structure of the clusters. Subsequently, a linear regression was performed to identify and remove the possible *outliers* through the Mahalanobis distance.

After finalizing this step, cluster analysis was conducted with the objective of grouping the elderly with similar inflammatory characteristics. For this, the clustering algorithm was used through the *k-means* method with the objective of finding a data partition with reduced Euclidean distance to the center of the cluster, aiming to form homogeneous groups from the predetermined characteristics of the zinc, interleukin-6, and tumor necrosis factor α levels.

In this process, a pertinent number of three clusters was verified, considering that for these conglomerates, each cluster had n>30. After the creation or identification of the clusters of the inflammatory state of the study subjects, the parametric status of the independent variables was confirmed by the *Kolmogorov-Smirnov* test, and the ANOVA test with Bonferroni post hoc or *Kruskal-Wallis*, followed by the Mann-Whitney test with penalization, was carried out to compare the variables (biochemical, anthropometric, and sociodemographic, and health of the elderly) between the clusters. The chi-squared test was used to verify the association between the qualitative variables, sex, type of LSIE, polypharmacy, multi-morbidities, and clusters. The multicollinearity of the variables that obtained a value of $p < 0.20$ in these analyses was tested, and then an ordinal logistic regression was performed for a 95% confidence level.

Results

Of the nine institutions participating in the study, five were not for-profit and four were for-profit. Of a total of 304 elderly, 24 elderly or their guardians refused to participate in the study, and 71 participants were excluded because they met some of the exclusion criteria. Additional elderly participants were excluded (n = 7) who presented extreme values (coefficient variation error) of biochemical variables (*outliers*) or did not perform all evaluations (n = 24). Prior to the grouping of the elderly according to characteristics of their inflammatory state, the data were analyzed to confirm the validity of the multivariate analysis, in which one individual was identified as an *outlier* (*Mahalanobis* Distance-D2) and eliminated from the sample, leaving a final sample of 187 individuals.

Three clusters (n> 30) were formed, presented in Table 1, which demonstrates the mean values and differences in the inflammatory variables for each group formed. When analyzing the variables used as a basis for the composition of the clusters, Zn (F = 116,83) showed the best discrimination between clusters, followed by IL-6 (F = 101,09) and TNF (F = 72,98). With respect to Cluster 1, higher concentrations of IL6 and TNFα were observed, associated with a low concentration of Zn, in relation to the other clusters. The increase in inflammatory cytokines associated with a reduction in zinc is related to the presence of *inflamm-aging* in this group of elderly individuals. Cluster 3 presented a characteristic antagonistic to cluster 1, with a lower concentration of IL6 and TNF and a higher concentration of Zn, with a low inflammatory load. The characteristics of cluster 2 were considered intermediate compared to the other clusters.

TABLES

Table 1. Characterization of the inflammatory state distributed into clusters formed by inflammatory cytokines and zinc in the plasma of institutionalized elderly.

Conglomerates	N	IL-6 (Pg/Ml)#	Tnfα (Pg/Ml)#	Zn (Ug/Dl)$	Cluster Description
Cluster 1	40	8.15 (6.8 -9.77) [a]	12.6 (9.8-14.8) [a]	76.27 (11.53) [a]	*Inflamm-aging*
Cluster 2	70	3.25 (2.2-4.8) [b]	5.1 (4.0-8.1) [b]	74.08 (8.60) [a]	Transient Inflammatory State
Cluster 3	77	2.9 (2.2-3.9) [b]	8.2 (4.9-8.7) [c]	98.11 (9.94) [b]	No *Inflamm-aging*
p-value		<0.001	<0.001	<0.001	

Note: IL-6 = Interleukin 6; TNFα = Tumor Necrosis Factor α; Zn = Zinc; **#:** Data are presented in median and interquartile range considering nonparametric data. **$:** The data are distributed in mean and standard deviation, considering the parametric data. a/b/c: Different letters indicate a statistically significant difference between the variables.

Defining the characteristics of the 3 clusters, the association between the independent variables and *inflamm-aging* and the independent variables was performed, in which it was possible to observe a difference (p <0.05) between the clusters for the variables total cholesterol, LDL, triglycerides, and creatinine (Table 2). The *inflamm-aging* cluster presented a higher level of total cholesterol, LDL, triglycerides, and creatinine in relation to the cluster without *inflamm-aging*, demonstrating the same antagonistic relation presented between the inflammatory markers. The Transient Inflammatory State cluster presented characteristics similar to the *inflamm-aging* cluster in the variables total cholesterol, LDL, triglycerides, and creatinine. The latter variable, in turn, also presented a similar response to the cluster without *inflamm-aging*, indicating a smaller effect in relation to the inflammatory variables present in each cluster.

Table 2- Association relationship between biochemical variables and inflammation-aging in institutionalized elderly.

Independent Variables #	***Inflamm-Aging*** **Mean (SD)**	**Transient Inflammatory State Mean (SD)**	**No *Inflamm-Aging*** **Mean (SD)**	***P-Value***
Total Cholesterol (Mg/Dl)	186. 23 (40.79) [a]	185.70 (39.52) [a]	149.56 (34.23) [b]	<0.001*
HDL (G/DL)	45.08 (7.63)	44.97 (10.19)	42.41 (9.93)	0.194
LDL (G/DL)	116.82 (37.56) [a]	113.84 (36.77) [a]	87.46 (31.55) [b]	<0.001*
Triglycerides (Mg/Dl)	121.85 (51.46) [a]	134.64 (53.1) [a]	98.60 (42.47) [b]	<0.001*
Urea (Mg/Dl)	40.5 (13.3)	41.3(15.7)	38.8(15.6)	0.607
Albumin (G/Dl)	3.58 (0.75)	3.64 (0.74)	3.46 (0.75)	0.334
Independent Variables $	**Cluster 1** **Median (IQR)**	**Cluster 2** **Median (IQR)**	**Cluster 3** **Median (IQR)**	***P-Value***
Total Proteins (Mg/Dl)	7.10 (6.4-7.8)	7.30 (6.9-7.7)	7.10 (6.6-7.7)	0.454
Creatinine (Mg/Dl)	1.0 (0.9-1.2) [a]	0.9 (0.8-1.1) [a/b]	0.9 (0.8-1.1) [b]	0.034

Note: **#:** Data are presented as the median and interquartile range considering nonparametric data. **$:** The data are distributed in mean and standard deviation, considering the parametric. **a/b/c:** Different letters denote a statistically significant difference between the variables. *p<0.05

In Table 3, it can be seen that elderly people living in for-profit LSIEs are predominantly in the Transient Inflammatory State (46.3%) and No *Inflamm-aging* (35.0%) clusters, whereas those residing in not for-profit LSIEs are predominantly in the cluster without *Inflamm-aging* (53.1%). Regarding the distribution by sex, male individuals are predominantly in the cluster without *inflamm-aging* (56.1%) in relation to the cluster with *inflamm-aging* (22%) and Transient Inflammatory State cluster (22%), while females are predominantly found in the cluster Transient Inflammatory State (41.8%) and the cluster without *inflamm-aging* (37.0%) in relation to the cluster with *inflamm-aging* (21.2%). In addition, there were no differences between clusters regarding BMI, age, number of morbidities, and polypharmacy.

Table 3. Association of *inflamm-aging* with sex, age, BMI, morbidities, polypharmacy, and type of LSIE of institutionalized elderly.

Variables*		***Inflamm-Aging*** **N (%)**	**Transient Inflammatory State N (%)**	**No** ***Inflamm-Aging*** **N (%)**	***P-Value***
SEX	Masculine	9 (22.0)	9 (22.0)	23 (56.1)*	0.045
	Feminine	31 (21.2)	61(41.8)	54 (37.0)	
BMI	Low Weight	17 (20.0)	28 (32.9)	40 (47.1)	0.663
	Eutrophic	13 (23.6)	22 (40.0)	20 (36.4)	
	Excess Weight	10 (21.3)	20 (42.6)	17 (36.2)	
Multimorbidities	≥ 3comorbidities	13 (18.8)	28 (40.6)	28 (40.6)	0.729
	≤ 2comorbidities	27 (22.9)	42 (35.6)	49 (41.5)	
Number of Medications	≥ 5 medications	21 (23.9)	34 (38.6)	33 (37.5)	0.581
	≤ 4 medications	19 (19.2)	36 (36.4)	44 (44.4)	
Type of LSIE	For profit	23 (18.7)	57 (46.3)*	43 (35.0)	0.002
	Not for profit	17 (26.6)	13 (20.3)	34 (53.1)*	
Age	<80 years	10 (14.1)	26 (36.6)	35 (49.3)	0.095
	≥80 years	30 (25.9)	44 (37.9)	42 (36.2)	

BMI = Body Mass Index; LSIE= Long-Term Institution for the Elderly.

* Chi-square test

When the ordinal logistic regression of the previously analyzed independent variables was performed, it was possible to observe the net effect of age, LDL, HDL, and triglycerides on inflammation (Table 4). The increase of 1 unit of measurement in LDL, HDL, and triglycerides increased the chance of inflamm-aging by 1.5%, 4.1%, and 0.9%, respectively (Cluster 3 to 1), while long-lived elderly people (≥80 years) had an 84.9% chance of presenting *inflamm-aging* in relation to non-long-lived elderly individuals (<80 years).

Table 4 – Ordinal logistic regression of independent variables in relation to Inflamm-aging

Inflamm-aging	Odds Ratio	Standard error	Z	p>[z]	CI95%
Age (≥80 years)	1.849	0.57	2.00	0.04	1.01-3.39
LDL (mg/dL)	1.015	0.01	3.66	<0.01	1.01-1.02
HDL(mg/dL)	1.041	0.02	2.60	0.01	1.01-1.07
Urea(mg/dL)	0.98	0.01	-1.25	0.21	0.96-1.01
Creatinine (mg/dL)	2.315	1.25	1.56	0.12	0.80-6.67
Triglycerides (mg/dL)	1.009	0.01	2.85	<0.01	1.00-1.01

Discussion

We initially observed that the multivariate technique of interdependence is a good way to evaluate the inflammatory pattern in the elderly and that the association between IL-6, TNF-α, and zinc are responsive markers for the diagnosis of *inflamm-aging*, for which, until now, there are no normative diagnostic values in the literature [37]. In addition, there were no differences between the clusters when comparing the prevalence of sarcopenic individuals. The elderly residents in not-for-profit LSIEs presented the best results regarding the *inflamm-aging* condition more frequently in the female sex. Concentrations of LDL, cholesterol, and triglycerides were higher in the *inflamm-aging* group. In the analysis of the net effect of the independent variables, a greater influence of age, HDL, LDL, and triglycerides was observed in the characterization of the *inflamm-aging* group.

The process of low-intensity chronic inflammation (*inflamm-aging*) results in a continuous increase in the production of pro-inflammatory cytokines, including IL-6 and TNFα [3–5]. For example, Xia et al. [37] propose that pro-inflammatory cytokines play a key role in the mechanism of *inflamm-aging*, with serum concentrations of IL-6 and TNFα markers representative of *inflamm-aging* [37]. When we observed the characteristics of cluster 1 in relation to the proinflammatory cytokines, we found higher values of IL-6 (8.15 pg/ml) and TNFα (12.6 pg/ml) than those observed in another study performed with young and elderly adults, both in IL-6 (2.57 pg/ml) and TNFα (4.94 pg/ml) [38]. In addition, the IL-6 values found in cluster 1 were lower when compared to severe inflammatory conditions such as sepsis (IL-6 = 64.1 pg/ml) and systemic inflammatory response syndrome (IL-6 = 41.1 pg/ml (43), a fact that classifies the

inflamm-aging cluster with low intensity inflammation. These results are very important to define the risk group to COVID-19 among institutionalized elderly, recognizing that patients who do not survive to this disease present higher values of IL-16 compared to patients who do not die [30].

In addition to the increase in the synthesis of proinflammatory cytokines triggered in *inflamm-aging* [1], the increase in bioavailability of zinc can be considered an important marker to characterize this condition due to the relationship presented with pro-inflammatory cytokines [39] of zinc in reducing the transcription of proinflammatory cytokines while favoring the transcription of anti-inflammatory cytokines [7,39]. This information is consistent with the results of zinc and its relationship with IL-6 and TNFα observed in the clusters. The plasma zinc values (76.27 µg/ml) observed in the *inflamm-aging* cluster were lower than those in the non-*inflamm-aging* cluster (98.11 ug/ml). In addition, zinc (F = 116,83) was the variable that best described the clusters, followed by IL6 (F = 101,09) and TNFα (F = 72,98), demonstrating the importance of inserting this marker in future studies aimed at identifying *inflamm-aging*, corroborating studies that point to this variable as an important modulator of inflammatory activity [39].

This analysis is very important because there is research that has already demonstrated that zinc has antiviral effects; improving immune responses and suppressing viral replication provide a protective role against the COVID-19 pandemic, likely by improving the host's resistance against viral infection [40].

In contrast to the *inflamm-a*ging cluster, the configuration of the proinflammatory and zinc cytokines in the cluster without *inflamm-aging* presents a framework with a lack of inflammation due to the reduced values of TNFα and IL-6 and high values of zinc. Mocchegiani et al. [39] defend the ability of pro-inflammatory cytokines to regulate the bioavailability of zinc observed in the clusters, justifying this antagonistic relationship between these two markers. The cluster with a transient inflammatory state presents characteristics of both clusters, in which the concentration of IL-6 was similar to that presented by the cluster without *inflamm-aging* and the zinc index was similar to that presented by the cluster with *inflamm-aging*, whereas the TNFα value presented an intermediate pattern between the other two clusters, being therefore characterized as a "transient inflammatory state".

The deficiency of zinc, common in the elderly [41], associated with increased secretion of inflammatory cytokines, also plays an important role in oxidative stress and endothelial cell apoptosis [6]. Cardiovascular diseases are associated with IL-6 and TNF-α, which in turn act in distinct but complementary ways [42]. IL-6 is considered an independent risk factor for the prothrombotic state, whereas TNF-α induces endothelium-dependent relaxation, interfering with the binding and transmigration of leukocytes through the endothelium [42]. The concentrations of IL-6 and TNF-α are associated with dyslipidemia, a factor that compromises endothelial function [5,7].

Systemic immune system dysregulation may be able to cause acute respiratory distress syndrome (ARDS) but multiple organ failure and finally lead to death in severe cases of SARS-CoV-2 infection.

Therefore, inflammatory biomarker dosage is also part of preliminary guidelines for the diagnosis and treatment of coronavirus 2 (SARS-CoV-2) infection [43].

In addition, zinc deficiency alters key transcription factors and adhesion molecules at LDL receptors, increasing the risk of hypertriglyceridemia, which reinforces the deleterious context for cardiovascular health [6,39]. These findings may explain the greater net effect of LDL and triglycerides on *inflamm-aging* compared to other biochemical variables and reinforce the theory of endothelial injury as a theoretical model to elucidate chronic inflammation with a low intensity characteristic of *inflamm-aging* [44,45]. Regarding HDL, although contradictory, the increase in its plasma concentration was also associated with *inflamm-aging* in the ordinal logistic regression model. This is because all groups presented reduced HDL values, with a slightly reduced mean in the cluster without *inflamm-aging*, which was already expected due to their overall reduction in cholesterol and LDL concentrations.

This framework of association with the *inflamm-aging* process is evidenced in the results of the present study, which demonstrated that individuals with *inflamm-aging* present higher amounts of LDL, triglycerides, and total cholesterol, resulting in an increased risk of endothelial injury [42]. This probably happens considering that the small increases in the concentrations of LDL, triglycerides, and total cholesterol are able to promote greater infiltration of lipoproteins in the arterial walls, generating accumulation and, consequently, endothelial injury [46]. In cluster 2, the proinflammatory cytokines presented lower values compared to cluster 1, a fact that did not occur in the variables related to the lipid profile. This indicates that the concentrations of LDL and triglycerides in cluster 2 resulted in better regulation of TNF-α and IL-6 by the immune system due to the action of anti-inflammatory cytokines (e.g., IL-10) or in a shorter time of exposure to an unresolved inflammatory state in relation to the *inflamm-aging* cluster, since zinc was similar between these clusters.

This association of blood fat levels with inflammaging becomes even more serious when we consider that the presence of cardiovascular disease is associated with a worse prognosis and mortality for COVID-19 [47]. In practical terms, a study by [48] reported an almost two-fold increase in mortality in patients with cardiovascular disease. With regard to the relationship between inflamm-aging and COVID-19, we can highlight that understanding this inflammatory condition is fundamental for the identification of elderly people with a higher risk of mortality if they are exposed to the virus. The scientific community [47,49,50] has proposed that the course of treatment and prognosis of COVID-19 should be stratified according to the presence or absence of comorbidities prior to SARS-COV-2 infection. Thus, those patients who have acute respiratory failure syndrome (SIRA), a characteristic symptom of COVID-19 but do not have any comorbidities, are stratified into TYPE A patients. Those who, in addition to SIRA, also have some comorbidities are classified as TYPE B. Finally, those classified as TYPE C are those who additionally have multiple organ injuries [49]. Thus, the higher the classification, the worse the prognosis for the disease. Based on this, it is possible to assume that the elderly with inflammatory characteristics already have a worse prognosis.

Regarding the sociodemographic variables, we observed that cluster 3 presented predominantly male elderly (56.1%) and elderly with low socioeconomic status (53.1%). The greater presence of men in this cluster could be explained by the fact that women present a higher chronic inflammatory state in relation to men, justified by the reduction in the production of estrogen, a hormone with an anti-inflammatory protective effect, caused by menopause, which therefore increases the possibility of low intensity inflammatory conditions [51,52]. With respect to socioeconomic conditions, it is expected that elderly people residing in for-profit LSIEs will present a more debilitated global health state [53]. For the clusters *inflamm-aging* and transient inflammatory state, no great differences were observed that could characterize these clusters regarding their demographic condition. This corroborates the findings obtained for the biochemical and anthropometric measures, in which no differences were observed for these groups. Furthermore, because residency in the not-for-profit LSIE groups several socioeconomic classes in the same group, it is pertinent to seek new strategies for future studies, which use more precise data to analyze this variable, to differentiate individuals using the indicator that best stratifies socioeconomic condition.

Moreover, we can observe that long-lived elderly people (≥ 80 years old) had a greater influence on the characterization of *inflamm-aging*. This was expected, since it is an age group that presents greater factors of health aggravation. Long-lived elderly individuals have presented a higher prevalence of arterial hypertension [54], associated with higher cardiovascular risk and lower functional capacity [55]. In a study conducted with long-lived elderly Brazilians of both sexes, when analyzing 9 chronic noncommunicable diseases, a prevalence of 67.0% of multimorbidity was observed in long-lived elderly compared to those aged less than 80 years [56].

In addition, we can infer that long-lived elderly individuals (>80 years) who present a greater amount of fat in the blood may present a higher relative risk of death from COVID-19. Therefore, it is possible to suggest that mechanisms associated with endothelial injury are associated with inflamm-aging, serving as the basis for future studies on this condition in institutionalized elderly and prevention factors to reduce COVID-19 mortality. In this way, public health strategies should direct their efforts to the fight against the control of diseases associated with mechanisms promoting endothelial injuries, considering this as the main factor associated with *inflamm-aging.* In addition, studies should be performed that seek to establish other diagnostic values for the inflammatory condition of the elderly, especially those that chronically verify the effect of this condition on the health problems of the elderly. We suggest the analysis of biochemical markers in place of inflammatory markers as a way to lower the future costs of a preventive evaluation to groups at higher risk.

Conclusion

IL-6, TNFα and zinc were shown to be responsive markers for characterizing *inflamm-aging* in institutionalized elderly. Individuals with a high inflammatory state present higher concentrations or altered lipid profiles of HDL, LDL, and triglycerides in relation to individuals with a reduced inflammatory state, demonstrating the association of the lipid profile with *inflamm-aging*. With regard to

sociodemographic aspects, it was observed that long-lived elderly people showed the greatest influence from *inflamm-aging.* As a way to reduce the mass genocide of institutionalized elderly people, those who have the aforementioned characteristics must remain in maximum social isolation.

Declarations

Conflicts of interest: None declared.

Declaration: All experiments were performed in accordance with relevant guidelines and regulations.

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