Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

IL-6 and TNF-α as Predictors of Mortality in Octogenarians: Evidence from a Brazilian Cohort

Ingridy Fátima Alves Rodrigues
ingridy.rodrigues@a.ucb.br

Universidade Católica de Brasília
Audrey Cecília Tonet-Furioso
Universidade Católica de Brasília
Flávia Maria Campos de Abreu
Universidade Católica de Brasília
Otávio Toledo Nóbrega
University of Brasília
Karla Helena Coelho Vilaça e Silva
Universidade Católica de Brasília

Research Article

Keywords: Aging. Immunosenescence. Cytokines. Mortality. Octogenarians

Posted Date: March 27th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-8818082/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

Inflammaging—characterized by chronic low-grade inflammation associated with aging—has been consistently linked to an increased risk of mortality, with cytokines acting as central mediators of this process. Therefore, investigating biomarkers capable of predicting outcomes in the oldest-old becomes particularly relevant, especially among Brazilian older adults, whose sociodemographic and health contexts differ from those observed in developed countries. Accordingly, this study aimed to evaluate whether inflammatory cytokines predict mortality in individuals aged 80 years and older, based on a retrospective Brazilian cohort. Between 2016 and 2018, sociodemographic and anthropometric variables were collected, and peripheral blood samples were obtained to measure inflammatory and anti-inflammatory cytokines. In 2024 and 2025, mortality occurrence was ascertained through information from family members and caregivers, copies of death certificates, interviews, and consultation of the National Registry of Deceased Individuals. In univariate Cox regression models, each unit increase in TNF-α concentration was associated with a 30% increase in mortality risk, while each unit increase in IL-6 levels was associated with a 1% increase in the risk of death, suggesting the potential utility of these cytokines as prognostic biomarkers in the oldest-old.

Introduction

Population aging poses challenges and increasing demands for the care of older adults and the promotion of healthy longevity, particularly among individuals aged 80 years and older (PAHO, 2023). In this context, predictors of chronic diseases and mortality based on circulating biomolecules are highly desirable due to their utility in refining risk scores and advancing the understanding of disease pathophysiology. Inflammatory biomarkers deserve particular attention because of their involvement in the development of numerous chronic conditions and in mortality outcomes. Inflammatory processes, including inflammaging, are associated with a higher prevalence of aging-related diseases, which rank among the leading causes of death (Baune et al., 2010).

Chronic low-grade inflammation, referred to as inflammaging, is recognized as a hallmark of biological aging (Tartiere, Freije, López-Otín, 2024) and, per se, confers increased susceptibility to a range of disorders, including cancer, osteoporosis, sarcopenia, depression, and dementia, as well as physical and cognitive disabilities. Although understood as an adaptive, multifactorial, and dynamic mechanism in response to cumulative antigenic stress throughout life (Fulop et al., 2018), this persistent inflammatory process disrupts systemic homeostasis and promotes the accumulation of cellular damage that contributes to frailty and premature death (Ferrucci & Fabbri, 2018). While inflammaging is characterized by persistent subclinical alterations in circulating levels of different classes of immunological mediators —including chemokines, regulatory and growth factors, and pro- or anti-inflammatory cytokines—pro-inflammatory cytokines appear to contribute more substantially to mortality risk, particularly among the oldest-old (PAHO, 2023; Panela & Ma, 2024; Tylutka, Walas, & Zembron-Lacny, 2024).

During the COVID-19 pandemic, for example, altered levels of IL-6 and TNF-α were identified as predictors of mortality among affected adults (Mandel et al., 2020), highlighting the need to improve or enhance immune health to increase resistance to infectious diseases in older adults (Teissier, Boulanger, & Cox, 2022).

Although chronic inflammation associated with aging underlies the development of age-related disorders, the possibility that specific levels of immunomarkers are associated with adverse outcomes such as frailty and mortality remains insufficiently explored. Moreover, both elevated and reduced levels may exacerbate these risks, particularly among the oldest-old (Fulop et al., 2018).

Therefore, in light of the considerations above, this study aimed to investigate the association between levels of inflammatory cytokines as predictors of mortality or longevity among individuals aged 80 years and older.

Methods

This analytical, comparative, retrospective cohort study was conducted based on two data collection phases. The first phase took place between 2016 and 2018 and included participants aged 80 years and older at baseline. During this phase, sociodemographic variables, anthropometric measurements, and peripheral blood samples were collected from 222 individuals for cytokine quantification at a laboratory facility. Details regarding recruitment procedures, blood sample collection, and clinical assessments have been described in previous studies (Neri et al., 2023; Filho et al., 2025; Amorim et al., 2021; Rodrigues et al., 2021).The second phase of the study was conducted between 2024 and 2025, during which mortality among participants enrolled in the first phase was ascertained based on interviews with family members and/or caregivers, as well as through access to death certificates or consultation of the National Registry of Deceased Individuals.

Serum samples obtained during the baseline phase were stored at − 80°C until thawed for the analysis of immunological mediators. Concentrations of interferon-gamma (IFN-γ), interleukin-2 (IL-2), IL-4, IL-6, IL-10, and tumor necrosis factor-alpha (TNF-α) were measured using a multiplex flow cytometry–based assay, employing a bead-based immunoassay kit (Human TH1/TH2 CBA Cytokine Kit II) manufactured by BD Biosciences® (San Diego, CA, USA). Serum samples were processed according to the manufacturer's protocol, and data acquisition was performed by recording a minimum of 300 events per cytokine bead on a BD FACSVerse flow cytometer using the FL4 channel. Data were analyzed using FCAP software, version 3.0 (BD Biosciences®, San Diego, CA, USA). Standard curves for each cytokine were generated using the mediator standard mixture provided by the manufacturer, and cytokine concentrations in serum samples were determined by interpolation from the corresponding standard curves.

Data analysis was conducted in three sequential steps to evaluate baseline levels of the cytokines IFN-γ, TNF-α, IL-10, IL-6, IL-4, and IL-2 as potential predictors of mortality during the period between the two study phases. Initially, descriptive analyses of the study variables were performed. For continuous

variables, measures of central tendency and dispersion were calculated, including mean, standard deviation, percentiles, median, minimum, and maximum values. Categorical variables were summarized using absolute frequencies and proportions. Adherence to normality assumptions was assessed using the Shapiro–Wilk test, in accordance with recommendations from the nonparametric statistics literature (Conover, 1999).

Survival analysis was performed using the Kaplan–Meier estimator (Kleinbaum & Klein, 2005). Follow-up time was calculated from the date of assessment at the first wave until death or the last contact with surviving participants. To identify predictors of mortality, the classical Cox proportional hazards model was applied, which estimates the effect of each predictor on time to event through hazard ratios, under the assumption of proportional hazards over the follow-up period. Estimation was based on partial likelihood, without parametric specification of the baseline hazard function. Analyses were conducted using the coxph() function from the **survival** package (Therneau, 2024) in R software, version 4.5.1 (R Core Team, 2025).

The study was conducted in accordance with ethical and scientific principles as established by Brazilian Ministry of Health Resolution No. 466, of December 12, 2012, and in compliance with the principles of the General Data Protection Law (LGPD) (Brazil, 2018). All responses were recorded in the REDCap (Research Electronic Data Capture) digital platform, with restricted access. The first phase of the project was approved by a Research Ethics Committee (REC) under approval number 1.185.879, and the second phase of data collection received approval from a Research Ethics Committee under approval number 6.603.725.

In both phases of the study, participation was voluntary. All participants were fully informed about the study objectives, as well as the potential risks and benefits, and provided written informed consent prior to enrollment.

Clinical trial number: not applicable.

Results

The final analytical sample comprised 129 participants, most of whom were female (62%) and self-identified as White (60%). After the sample losses described in Figure 1, 37 participants survived and 92 died during the follow-up period.

Initially, the sociodemographic characteristics of the sample were analyzed according to mortality status (survivors and deceased). Among surviving individuals (N = 37), 24 were female (64.9%) and 13 were male (35.1%), with a median age of 91 years (range: 85–98 years). Among participants who died during follow-up (N = 92[1]), 56 were female (60.9%) and 36 were male (39.1%), with a median age of 85 years (range: 78–101 years) (Table 1).

Table 1 Sociodemographic characteristics according to mortality status. Brasília, 2025

Variables	Survivors (N = 37)	Deceased (N = 92)
Sex		
Female	24 (64.86)	56 (60.87)
Male	13 (35.14)	36 (39.13)
Age (years)	91.00 (85.00; 98.00)	85.00 (78.00; 101.00)
Marital status		
Married	10 (27.03)	8 (8.79)
Single	27 (72.97)	83 (91.21)
(Missing data)	0	1
Race/ethnicity (IBGE classification)		
Asian	0 (0.00)	2 (2.20)
White	16 (43.24)	61 (67.03)
Indigenous	5 (13.51)	1 (1.10)
Brown (Pardo)	16 (43.24)	25 (27.47)
Black	0 (0.00)	2 (2.20)
(Missing data)	0	1
Weight (kg)	62.70 (30.00; 86.10)	60.20 (37.00; 88.60)
(Missing data)	0	19
Height (cm)	155.00 (137.00; 175.00)	156.00 (133.00; 178.00)
(Missing data)	0	19
Body mass index (kg/m²)	25.50 (13.70; 38.22)	25.56 (15.16; 35.47)
(Missing data)	0	19

Legend: n (%); Median (Min; Max)

Next, baseline cytokine concentrations were compared between survivors and deceased participants (Table 2). From a descriptive perspective, median levels of IFN-γ, TNF-α, IL-6, and IL-2 were numerically higher in the deceased group, whereas IL-10 and IL-4 showed very similar median values between groups.

It is important to note that missing data were present for IFN-γ, IL-10, IL-6, IL-4, and IL-2 measurements, corresponding to 9 surviving participants and 19 deceased participants, as well as for TNF-α

measurements, which were missing for 10 survivors and 21 deceased participants. These losses occurred due to inability to attend laboratory collection or insufficient sample volume for analysis.

Table 2 Baseline cytokine concentrations according to mortality status. Brasília, 2025

Variables	Survivors (N = 37)	Deceased (N = 92)
IFN-γ	5.67 (3.88; 11.05)	6.27 (3.70; 30.46)
TNF-α	1.45 (0.41; 3.55)	1.80 (0.27; 6.28)
IL-10	3.48 (2.30; 4.82)	3.39 (2.09; 394.00)
IL-6	4.20 (0.34; 23.86)	5.57 (0.13; 168.45)
IL-4	1.92 (0.13; 5.23)	1.66 (0.23; 4.81)
IL-2	8.95 (8.00; 17.83)	9.01 (8.00; 838.00)

Legend: n (%); Median (Min; Max).

Note: Data are presented as median (minimum; maximum). N indicates the number of participants per group. Missing values are reported by variable.

Survival analysis was performed using the Kaplan–Meier estimator, considering the time elapsed between the date of assessment at the first study phase and the date of death or the last contact with surviving participants. Figure 1 presents the cumulative overall survival of the sample, which was 14.1% at 9.038 years (95% CI: 3.4%–58.5%).

Finally, variables were individually tested using the Cox proportional hazards model (univariate Cox models) to assess the association of each variable with time to the event of death, based on the proportional hazards (PH) assumption, which evaluates the constancy of relative risk over time.

All variables included in the analyses met the proportional hazards assumption (Table 3).

Table 3 Univariate Cox proportional hazards models – variables meeting the proportional hazards assumption

Predictor	HR (95% CI)	p-value	N	Events
Female sex	0.82 (0.53; 1.28)	0.3883	119	82
Married marital status	0.46 (0.22; 0.95)	0.0371	118	81
White race	1.40 (0.89; 2.21)	0.1478	118	81
BMI (kg/m²)	0.97 (0.93; 1.02)	0.2869	103	66
TNF-α	1.30 (1.00; 1.68)	0.0482	90	63
IL-10	1.00 (1.00; 1.01)	0.1278	93	65
IL-6	1.01 (1.00; 1.02)	0.0359	93	65
IL-4	0.85 (0.65; 1.12)	0.2514	93	65
IL-2	1.00 (1.00; 1.00)	0.7033	93	65
IFN-γ	1.04 (0.97; 1.11)	0.2309	93	65

Note: Univariate Cox proportional hazards regression models (hazard ratio, HR) for mortality, including predictors that met the proportional hazards (PH) assumption.
95% CI = 95% confidence interval.
N = number of participants included in each model; Events = number of deaths observed.
BMI = body mass index.

Cytokines refer to baseline concentrations.

In univariate Cox proportional hazards analysis, three variables showed a statistically significant association with mortality: being married (HR = 0.46; 95% CI: 0.22–0.95; p = 0.037), TNF-α (HR = 1.30; 95% CI: 1.00–1.68; p = 0.048), and IL-6 (HR = 1.01; 95% CI: 1.00–1.02; p = 0.036). Married marital status was associated with a lower risk of death, whereas higher baseline concentrations of TNF-α and IL-6 were associated with an increased mortality risk. The remaining variables were not significant predictors of mortality.

Discussion

The variables identified as predictors of mortality (TNF-α and IL-6) are consistent with the inflammaging paradigm, as they demonstrate an association between pro-inflammatory cytokines and poorer prognosis, namely death. Increased serum concentrations of TNF-α and IL-6 were associated with a higher risk of mortality, whereas being married emerged as a protective factor against death.

Inflammaging alters immune responses with advancing age, leading to a weakened adaptive immune response and a chronically activated innate immune system, which is reflected in increased levels of pro-inflammatory cytokines (Tylutka, Walas, & Zembron-Lacny, 2024).

In the present study, elevated baseline concentrations of TNF-α were identified as predictors of mortality among octogenarians. TNF-α is a key pro-inflammatory cytokine and one of the most important mediators of the immune response. When present at elevated levels, TNF-α has been associated with increased severity of several cardiovascular diseases, which are recognized as the leading causes of death worldwide (Rolski et al., 2023).

TNF-α also plays a relevant role in tumor initiation and progression, as well as in the development of autoimmune diseases (Chu, 2013). In addition, it is involved in metabolic disorders, atherosclerosis (Fard et al., 2021), and coronary artery disease (Pu et al., 2007). In bone tissue, TNF-α is closely associated with skeletal disorders, including osteoporosis, fracture healing, intervertebral disc pathologies, cartilage degeneration, and rheumatoid arthritis (Yao et al., 2024).

Several therapeutic approaches have been investigated with the aim of modulating the immune response and enhancing immune resilience against age-related alterations (Nguyen & Cho, 2025). However, to date, the results of anti–TNF-α therapy in cardiac conditions have been inconsistent and remain controversial (Rolski et al., 2023).

TNF-α was among the first pro-inflammatory cytokines to be associated with cardiac diseases. Both cardiomyocytes and macrophages are capable of producing TNF-α, which acts through autocrine and paracrine mechanisms, contributing to the persistence of myocardial inflammation (Zhang & Dhalla, 2024).

Similar to the present study, Bruunsgaard et al. (2003), in a Danish cohort, identified TNF-α as a prognostic marker of mortality and frailty among 126 centenarians, whereas IL-6 did not affect survival. Conversely, Giovannini et al. (2011), in an Italian study involving 362 octogenarians, reported that elevated IL-6 levels were associated with a significantly higher risk of death, while TNF-α levels were not significantly related to the outcome. These findings highlight the heterogeneous impact of inflammaging-related biomarkers on longevity across different populations.

IL-6 is a cytokine with both anti-inflammatory and pro-inflammatory functions (Scheller et al., 2011; Amin et al., 2020), although it is classically regarded as a pro-inflammatory cytokine (Zhang & Dhalla, 2024). Significantly elevated levels are commonly observed in older adults with chronic diseases. Notably, IL-6 is also produced by skeletal muscle and its circulating concentrations may vary in response to physical activity (Tylutka, Walas, & Zembron-Lacny, 2024).

Its association with atherosclerosis is well established, with increased circulating levels linked to both the development and severity of the disease (Zhang & Dhalla, 2024). In addition, elevated IL-6 levels have been associated with obesity and insulin resistance, as this cytokine is also produced by adipose tissue (Abbatecola et al., 2004). Furthermore, during the recent SARS-CoV-2 pandemic, IL-6 emerged as a predictor of mortality among adults with COVID-19 (Rosyid et al., 2024).

In the present study, elevated IL-6 levels were identified as predictors of mortality among octogenarians, in agreement with findings from a large U.S. cohort study involving 1,122 middle-aged adults (mean age 47.8 years), in which this association was observed to be significantly stronger in women than in men (Hooten et al., 2023).

Additionally, this cohort study including octogenarians and nonagenarians demonstrated a protective effect of marriage on all-cause mortality. Being married or living with a partner was associated with a lower risk of death. These findings are consistent with a prospective cohort study using data from the U.S. National Health and Nutrition Examination Survey, which included older adults aged 60 years and older and showed that being married, living with a partner, or being separated was associated with a lower risk of mortality compared with individuals who had never married (Wang & Yi, 2023). This evidence highlights marital status as a favorable condition for better health across multiple dimensions, reinforcing the positive relationship between marriage and survival.

Conversely, a Danish cohort study found that widowhood was associated with increased mortality in older age for both men and women when compared with married individuals (Blanner et al., 2020). However, widowhood was associated with more favorable outcomes than divorce regarding the onset of cognitive impairment in a cohort of older adults in the United States (Liu et al., 2019).

The present study has as a limitation the reduction in sample size from the initial cohort (n = 221) to the final analytical sample (n = 129). However, attrition is inherent to longitudinal studies involving older populations and is primarily driven by death, worsening health conditions, disabilities that preclude continued participation, loss to follow-up, or refusal. Such losses are strongly associated with both follow-up duration and advanced age of participants.

In this context, Okpara et al. (2023), in a cohort study following women aged 55 years and older for approximately six years, reported an attrition rate of 30.2%. Similarly, Jacobsen et al. (2021), in a 10-year cohort study including participants aged 65 years and older, observed an attrition rate of 77% by the end of the follow-up period.

Therefore, the cumulative sample attrition observed in the present study falls within the range expected for cohorts involving the oldest-old and does not constitute an atypical finding or one incompatible with the longitudinal design adopted. This attrition should be interpreted in light of the baseline characteristics of the sample and the epidemiological context of advanced aging.

Among the strengths of this study is the follow-up of a Brazilian cohort of octogenarians, a population that remains underrepresented in the scientific literature, particularly in middle-income countries. The assessment of inflammatory markers (IL-6 and TNF-α) in very old individuals contributes to a better understanding of the biological mechanisms associated with mortality at advanced ages. Given the scarcity of studies including populations aged 80 years and older, the analysis of these biomarkers allows for the exploration of the role of chronic low-grade inflammation in extreme aging and its

relationship with clinically relevant outcomes, thereby expanding the scientific evidence in an age group that is still poorly represented in the literature.

Conclusion

The present study demonstrated a positive association between elevated levels of the cytokines IL-6 and TNF-α and mortality among very old adults, and additionally showed a protective effect of marital status on this outcome.

IL-6 and TNF may be associated with multiple health conditions in very old adults that predispose to mortality. Therefore, these cytokines can be considered important mediators of different prognostic trajectories and likely predictive biomarkers of mortality in this population, potentially contributing to future clinical assessments and guiding therapeutic decision-making.

The findings provide relevant evidence to support the discussion on the role of systemic inflammation in advanced aging and may inform future investigations and care strategies targeted at this age group. Future research should consider longitudinal follow-up with repeated measurements of the assessed cytokines in order to evaluate their trajectories over time, as well as the influence of comorbidities and health-related events throughout advanced aging. In addition, the inclusion of nutritional, cognitive, and frailty-related variables, along with the monitoring of lifestyle behaviors and clinical interventions, may contribute to the development of more robust predictive models of mortality.

Abbreviations

APS
Primary Health Care
BMI
Body Mass Index
CBA
Cytometric Bead Array
CI
Confidence Interval
CNPq
National Council for Scientific and Technological Development
DCNT
Chronic Non-Communicable Diseases
HR
Hazard Ratio
IFN-γ
Interferon-gamma
IL-2

Interleukin-2
IL-4
Interleukin-4
IL-6
Interleukin-6
IL-10
Interleukin-10
SASP
Senescence-Associated Secretory Phenotype
TNF-α
Tumor Necrosis Factor-alpha

Declarations

Ethics approval and consent to participate

This study was approved by the Research Ethics Committee of the Universidade Católica de Brasília (Comitê de Ética em Pesquisa da Universidade Católica de Brasília), approval number 6.603.725, in accordance with the Declaration of Helsinki and Brazilian ethical regulations.

All participants provided written informed consent at baseline assessment.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to ethical and privacy restrictions involving older adults but are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This study was supported by the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq).

The funding body had no role in the design of the study; collection, analysis, and interpretation of data; or in writing the manuscript.

Authors' contributions

IFAR conceived and designed the study, defined the research question, conducted the literature review, performed data collection and analysis, and drafted the final manuscript.

ACTF provided technical and logistical support, overseeing the laboratory analyses and contributing to the methodological description.

FMCA contributed to the writing and critical discussion of the results.

OTN critically reviewed the manuscript and suggested revisions where appropriate.

KHCVS supervised all stages of the research, performed the statistical analyses, and conducted the overall critical revision of the manuscript.

All authors read and approved the final manuscript.

Acknowledgements

The authors thank all participants and their families for their valuable contribution to this study. The authors also acknowledge the support of the research and laboratory teams involved in data collection and cytokine analyses.

Conflicts of Interest and Funding

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

This work was funded by the Brazilian National Council for Scientific and Technological Development (CNPq), Call for Proposals No. 21/2023, Grant No. 382958/2025-0.

References

1. Abbatecola AM, Ferrucci L, Grella R, Bandinelli S, BonafÃ¨ M, Barbieri M, et al. Diverse Effect of Inflammatory Markers on Insulin Resistance and Insulin-Resistance Syndrome in the Elderly. J Am Geriatr Soc. 2004;52(3):399–404.
2. Amin MN, Siddiqui SA, Ibrahim M, Hakim ML, Ahammed MS, Kabir A et al. Inflammatory cytokines in the pathogenesis of cardiovascular disease and cancer. SAGE Open Med [Internet]. 2020;8(8):205031212096575. Available from: https://journals.sagepub.com/doi/full/10.1177/2050312120965752
3. Amorim DNP, Nascimento DC, Stone W, Alves VP, Moraes CF. SIlva KHCVi. Muscle Quality Is Associated with History of Falls in Octogenarians. J Nutr Health Aging. 2020;25(1):120–5.

4. Baune BT, Rothermundt M, Ladwig KH, Meisinger C, Berger K. Systemic inflammation (Interleukin 6) predicts all-cause mortality in men: results from a 9-year follow-up of the MEMO Study. GeroScience [Internet]. 2010 Jul 9 [cited 2021 Aug 21];33(2):209–17. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC3127470/
5. Blanner C, Mejldal A, Prina AM, Munk-Jørgensen P, Ersbøll AK, Andersen K. Widowhood and mortality: a Danish nationwide register-based cohort study. Epidemiol Psychiatr Sci [Internet]. 2020 [cited 2026 Jan 23];29. Available from: https://www.cambridge.org/core/journals/epidemiology-and-psychiatric-sciences/article/widowhood-and-mortality-a-danish-nationwide-registerbased-cohort-study/8FCCDB77AC47DCBD22F9AA63BF0739ED
6. Brasil, LEI No 13.709, DE 14 DE AGOSTO DE. 2018 [Internet]. Planalto.gov.br. 2022. Available from: https://www.planalto.gov.br/ccivil_03/_ato2015-2018/2018/lei/l13709.htm
7. Bruunsgaard H, Andersen-Ranberg K, Hjelmborg JvB, Pedersen BK, Jeune B. Elevated levels of tumor necrosis factor alpha and mortality in centenarians. Am J Med [Internet]. 2003 Sep 1 [cited 2021 Feb 12];115(4):278–83. Available from: https://www.amjmed.com/article/S0002-9343(03)00329-2/fulltext
8. Conover WJ. Practical nonparametric statistics. Wiley; 1999.
9. Fard TK, Ahmadi R, Akbari T, Moradi N, Fadaei R, Kazemi Fard M, et al. Klotho, FOXO1 and cytokines associations in patients with coronary artery disease. Cytokine. 2021;141:155443.
10. Ferrucci L, Fabbri E. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. Nat Ver Cardiol [Internet]. 2018;15(9):505–22. Available from: https://www.nature.com/articles/s41569-018-0064-2
11. Filho ER, de Koeche A, Bueno C, Toledo FF, de Alves O, Silva VP. HS, Unraveling the intertwined threads of insomnia and sarcopenia in cognitive and functional impairment in octogenarians. BMC Geriatr [Internet]. 2025 Nov 7 [cited 2026 Jan 24];25(1):868–8. Available from: https://link.springer.com/article/10.1186/s12877-025-06398-3
12. Fulop T, Larbi A, Dupuis G, Le Page A, Frost EH, Cohen AA et al. Immunosenescence and Inflamm-Aging As Two Sides of the Same Coin: Friends or Foes? Front Immunol [Internet]. 2018;8. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5767595/
13. Giovannini S, Onder G, Liperoti R, Russo A, Carter C, Capoluongo E, et al. Interleukin-6, C-Reactive Protein, and Tumor Necrosis Factor-Alpha as Predictors of Mortality in Frail, Community-Living Elderly Individuals. J Am Geriatr Soc. 2011;59(9):1679–85.
14. Hooten NN, Mode NA, Allotey S, Ezike N, Zonderman AB, Evans MK. Inflammatory proteins are associated with mortality in a middle-aged diverse cohort. Clin Transl Med [Internet]. 2023 Sep 1 [cited 2025 Jun 5];13(9). Available from: https://www.eatingwell.com/best-herb-to-decrease-inflammation-11742975
15. Jacobsen E, Ran X, Liu A, Chang CCH, Ganguli M. Predictors of attrition in a longitudinal population-based study of aging. Int Psychogeriatr [Internet]. 2021 Aug 1 [cited 2026 Feb 1];33(8):767–78. Available from: https://www.cambridge.org/core/journals/international-

psychogeriatrics/article/abs/predictors-of-attrition-in-a-longitudinal-populationbased-study-of-aging/FDA94EA1D8CD57C8E3FD80C010DF8DB7

16. Kleinbaum DG, Klein M. Survival Analysis: A Self-Learning Text. 2ed ed. New York: Springer Science; 2005.
17. Liu H, Zhang Y, Burgard SA, Needham BL. Marital status and cognitive impairment in the United States: evidence from the National Health and Aging Trends Study. Ann Epidemiol [Internet]. 2019;38:28–34.e2. Available from: https://www.sciencedirect.com/science/article/abs/pii/S104727971930198X
18. Mandel M, Harari G, Gurevich M, Achiron A. Cytokine prediction of mortality in COVID19 patients. Cytokine. 2020;134:155190.
19. Neri AL, Arbex S, de Assumpção D, Yassuda MônicaS, Portella MR, Doring M et al. As características de saúde de octogenários recrutados em diferentes contextos evidenciam a heterogeneidade do envelhecimento. Estud Interdiscip Envelhec [Internet]. 2023 [cited 2025 Apr 22];28. Available from: https://seer.ufrgs.br/RevEnvelhecer/article/view/132938
20. Okpara C, Adachi JD, Papaioannou A, Ioannidis G, Thabane L. Exploring participant attrition in a longitudinal follow-up of older adults: the Global Longitudinal Study of Osteoporosis in Women (GLOW) Hamilton cohort. BMJ Open [Internet]. 2023 Jul 1 [cited 2026 Feb 1];13(7):e066594–4. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10373724/
21. OPAS - Organização Pan-Americana de Saúde. Envelhecimento Saudável - OPAS/OMS | Organização Pan-Americana da Saúde [Internet]. www.paho.org.2023. Available from: https://www.paho.org/pt/envelhecimento-saudavel
22. Pan Y, Ma L. Inflammatory markers and physical frailty: towards clinical application. Immun Ageing [Internet]. 2024 Jan 6 [cited 2024 Apr 22];21(1). Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC10770917/
23. Quynh T, Cho KA. Targeting immunosenescence and inflammaging: advancing longevity research. Exp Mol Med [Internet]. 2025 Sep 1 [cited 2026 Jan 30]; Available from: https://www.nature.com/articles/s12276-025-01527-9?utm_source=chatgpt.com
24. Rodrigues IFA, Alves VP, Gomes L, de Pereira O, Nóbrega DS, de Silva O. KHCV e. Associação entre eventos estressores e citocinas inflamatórias e anti-inflamatórias em pessoas idosas longevas. Rev Bras Geriatr Gerontol [Internet]. 2021;24(2). Available from: https://www.scielo.br/j/rbgg/a/VQxxqvcq59gxS7Gshvtc6YK/?lang=pt&format=pdf
25. Rolski F, Tkacz K, Węglarczyk K, Kwiatkowski G, Pelczar P, Jaźwa-Kusior A et al. TNF-α protects from exacerbated myocarditis and cardiac death by suppressing expansion of activated heart-reactive CD4 + T cells. Cardiovasc Res [Internet]. 2023 Oct 25 [cited 2024 Jul 30];120(1):82–94. Available from: https://academic.oup.com/cardiovascres/article/120/1/82/7329956#441708001
26. Scheller J, Chalaris A, Schmidt-Arras D, Rose-John S. The pro- and anti-inflammatory properties of the cytokine interleukin-6. Biochimica et Biophysica Acta (BBA) – Mol Cell Res [Internet].

2011;1813(5):878–88. Available from: https://www.sciencedirect.com/science/article/pii/S0167488911000425

27. Tartiere AG, Freije P, López-Otín C. The hallmarks of aging as a conceptual framework for health and longevity research. Front Aging [Internet]. 2024 Jan 15 [cited 2024 Mar 12];5. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10824251/
28. Teissier T, Boulanger E, Cox LS. Interconnections between Inflammageing and Immunosenescence during Ageing. Cells [Internet]. 2022 Jan 21 [cited 2026 Jan 23];11(3):359. Available from: https://pubmed.ncbi.nlm.nih.gov/35159168/
29. Tylutka A, Walas Ł, Zembron-Lacny A. Level of IL-6, TNF, and IL-1β and age-related diseases: a systematic review and meta-analysis. Front Immunol [Internet]. 2024;15. Available from: https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2024.1330386/full
30. Wang L, Yi Z. Marital status and all-cause mortality rate in older adults: a population-based prospective cohort study. BMC Geriatr [Internet]. 2023 Apr 4 [cited 2026 Jan 23];23(1). Available from: https://link.springer.com/article/10.1186/s12877-023-03880-8
31. Yao Q, He L, Bao C, Yan X, Ao J. The role of TNF-α in osteoporosis, bone repair and inflammatory bone diseases: A review. Tissue Cell [Internet]. 2024 Jun 27 [cited 2026 Jan 30];89:102422. Available from: https://www.sciencedirect.com/science/article/pii/S004081662400123X
32. Zhang H, Dhalla NS. The Role of Pro-Inflammatory Cytokines in the Pathogenesis of Cardiovascular Disease. Int J Mol Sci [Internet]. 2024 Jan 16 [cited 2024 Mar 10];25(2):1082–2. Available from: https://www.mdpi.com/1422-0067/25/2/1082#B9-ijms-25-01082

Figures

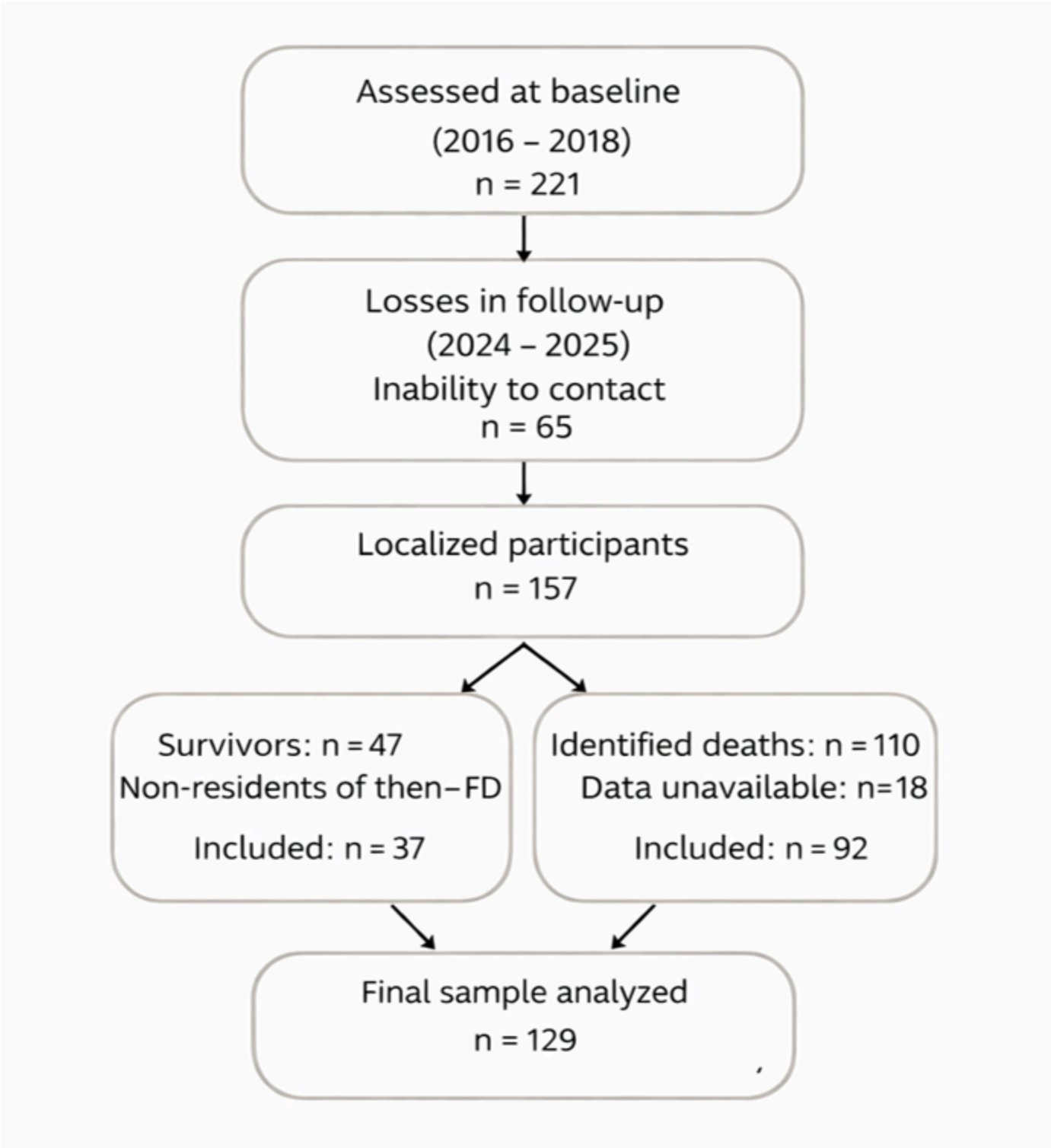


Figure 1

Participant flow, follow-up losses, and composition of the final sample

Identification, eligibility, exclusion, and inclusion stages of participants, illustrating the flow toward the final analytical sample of the study.

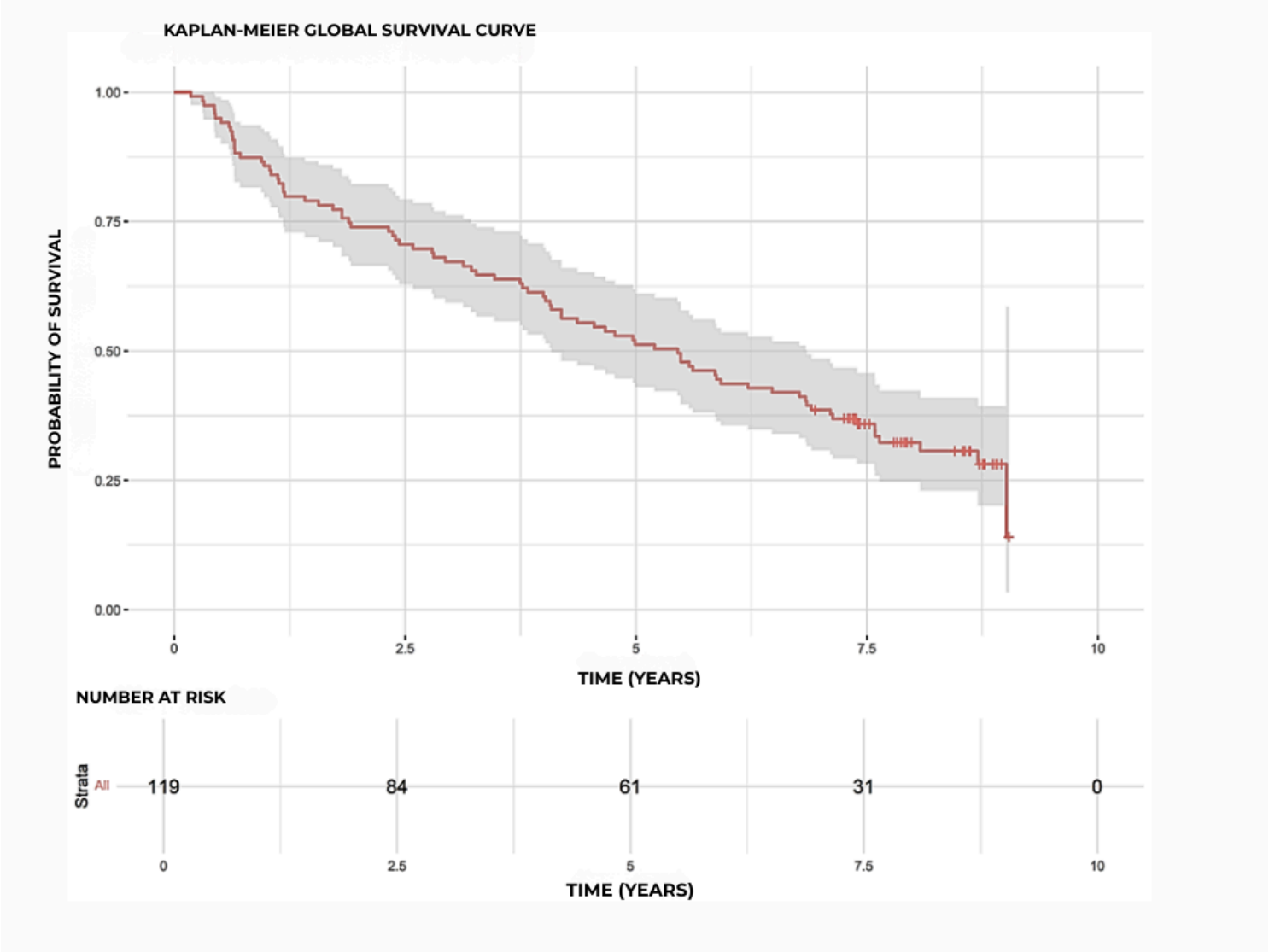


Figure 2

Overall Kaplan–Meier survival curve

Overall Kaplan–Meier survival curve of the study population, showing cumulative survival probability over time (years). Shaded areas represent 95% confidence intervals, and tick marks indicate censored observations. The number of participants at risk at each time point is displayed below the curve.