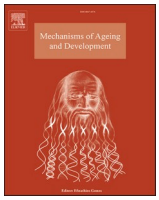
Mechanisms of Ageing and Development 215 (2023) 111872

Contents lists available at ScienceDirect

Mechanisms of Ageing and Development

journal homepage: www.elsevier.com/locate/mechagedev



The influence of inflammation and frailty in the aging continuum

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ARTICLE INFO

Keywords:
Aging
Inflammaging
Frailty
Neuroinflammation
Cytokines

ABSTRACT

Inflammaging is a low-grade inflammatory state that can be considered an adaptive process aimed at stimulating appropriate anti-inflammatory response. Frailty is determined by the accumulation of molecular and cellular defects accumulated throughout life; therefore, an appropriate frailty computation could be a valuable tool for measuring biological age. This study aims to analyse the association between inflammatory markers and both chronological age "per se" and frailty. We studied 452 persons aged 43–114 years. A Frailty Index (FI) was computed considering a wide range of age-related signs, symptoms, disabilities, and diseases. Plasma concentrations of inflammatory cytokines and peripheral markers of neuroinflammation were analysed by next-generation ELISA. The mean age of the cohort was 79.7 (from 43 to 114) years and the median FI was 0.19 (from 0.00 to 0.75). The concentrations of most inflammatory markers increased significantly with chronological age, after adjustment for sex and FI. Interferon-γ was significantly affected only by FI, while interleukin (IL)-10 and IL-1β were associated only with chronological age. In conclusion, we described different associations between inflammatory components and chronological vs. biological age. A better characterization of the molecular signature of aging could help to understand the complexity of this process.

1. Introduction

The number of older persons is steadily increasing worldwide (United Nations). The increase in average life span has however been associated with an increase in age-related chronic diseases. Thus, understanding the mechanisms that regulate the aging process is crucial for the comprehension of the causal mechanisms of age-related diseases and for studying tailored interventions.

Aging and age-related diseases share several biological mechanisms, the so-called "hallmarks of aging," as proposed by López-Otín et al. (2013) and recently reviewed by Schmauck-Medina et al. (2022). Interestingly, they are closely interconnected with each other, and inflammation could represent the biological "umbrella" that encloses all of them (Schmauck-Medina et al., 2022).

In fact, aging is characterized by a progressive impairment of immune cell functions, a phenomenon called "immunosenescence", which affects natural and acquired immunity (Barbé-Tuana et al., 2020; De Martinis et al., 2005; Franceschi et al., 1995). For a long time, it has been considered detrimental since it causes "inflammaging" which consists in a low-grade inflammatory status (Cevenini et al., 2013), although inflammaging can be considered an adaptive process designed to stimulate an appropriate anti-inflammatory response necessary to counterbalance the environmental changes related to the aging process itself (Fulop et al., 2020; Monti et al., 2017).

The balance between inflammaging and "anti-inflammaging" is continuously remodelled as result of genetic background and environment exposure (Franceschi et al., 2007). This balance determines the outcome: longevity (centenarians) or pathological aging burdened with aging-related diseases.

Studies in the literature on cytokine levels and their association with aging have provided mixed results (Tran Van Hoi et al., 2023). Indeed, while there is consensus on the age-related increase in tumour necrosis factor (TNF)-α as well as interleukin (IL)-6 (Justice et al., 2018; Puzianowska-Kuźnicka et al., 2016), conflicting results have been reported for

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https://doi.org/10.1016/j.mad.2023.111872
Received 5 July 2023; Received in revised form 1 September 2023; Accepted 7 September 2023
Available online 8 September 2023

other pro-inflammatory cytokines, such as IL-1β, and especially for anti-inflammatory cytokines (e.g., IL-10) (Xu et al., 2022).

As a matter of fact, aging is characterized by the continuous adaptation of the organism to life-long exposure to physical, psychological and social stressors that finally leads to a relevant clinical complexity (Tiesler, 1988; Franceschi et al., 2000b). In this frame, the immune system reflects everyone's exposure to stress. This whole concept was underlined with the example of IL-6, which sometimes increases to extraordinarily high levels in centenarians, but whose consequences are very different from one individual to another (Baggio et al., 1998; Fagiolo et al., 1993).

Interestingly, the concept of frailty defines a condition characterized by increased vulnerability to stressors and reduced homeostatic reserves (Clegg et al., 2013). This condition is globally driven by the gradual, lifelong accumulation of molecular and cellular defects that impact on different organs and systems (e.g., skeletal muscle, brain, respiratory, cardiovascular, and endocrine systems) (Clegg et al., 2013; Kamwa et al., 2021).

For all these reasons, frailty is an excellent indicator of the physiological decline of individuals, and an appropriate calculation of frailty could be a valuable tool for measuring biological age (Buta et al., 2016; Angioni et al., 2022; Takeda et al., 2020).

Unfortunately, there are few studies that have investigated "inflammaging" and "anti-inflammaging" in relation to frailty experienced by old and very old people (Arosio et al., 2019; Franceschi et al., 2000a; Vasto et al., 2007; Rockwood and Mitnitski, 2007), and this may be the cause of the conflicting results obtained. Moreover, in nature there is a complex system that finely regulates cytokines activity on which the outcome of many biological processes depends.

Under these premises, the present study aims to analyse the cross-sectional association between inflammatory markers and chronological age "per se" and frailty as a valid tool for measuring biological age.

For this purpose, in a cohort of older persons that includes a fair number of very old people (centenarians), we measured classic cytokines and receptors belonging to the family of activated receptors expressed on myeloid cells (TREMs) as markers of neuroinflammation (Arts et al., 2013; Klesney-Tait et al., 2006).

2. Methods

2.1. Study design

Data are from a cohort study conducted in Northern Italy from 2012 to 2022 and funded by the Italian Ministry of University and Scientific Research. Those subjects with all the necessary information to compute a frailty index and with adequately bio-banked biological samples to perform the necessary evaluations were selected for this study. Overall, 452 people (315 women and 137 men) aged between 43 and 114 years were recruited.

At the time of enrolment, a trained multidisciplinary team administered a standardized and structured questionnaire to all participants to record information about their health, functions (i.e., Activity of Daily Living, ADL), cognition (i.e., Mini-Mental State Examination, MMSE), medications use, clinical history, and lifestyle (i.e., Body Mass Index, BMI) (Skytthe et al., 2011). Finally, depression was evaluated by using the Geriatric Depression Scale (GDS).

The biological samples from subjects affected by acute or chronic (i.e., Crohn's disease, ulcerative colitis, rheumatoid arthritis, psoriasis, lupus, asthma, autoimmune diseases and multiple sclerosis) inflammatory diseases were excluded, as well as from patients with a diagnosis of Alzheimer's disease (AD) (Dubois et al., 2014) and vascular dementia (Román et al., 1993), conditions that can affect inflammatory components.

The protocol received approval from the Ethical Committee of the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan (Prot. n. 2035, amendment 30/11/2011). All subjects who gave written informed consent to participate in the study and filled out the questionnaire were included in this study.

2.2. Frailty index

Frailty was measured through the frailty index (FI). The FI results from the count of various health deficits, including signs, diseases, disabilities, and biochemical parameters, as previously described (Searle et al., 2008). Briefly, the constituting variables were scored as 0 (absence of the deficit) or 1 (presence of the deficit). The FI was calculated as the ratio between the number of health deficits presented by the person and the total number of the health deficits considered for its computation (in our case, $n = 47$) (Arosio et al., 2019, 2020) (Supplementary Table).

The number in the denominator represents the number of variables available in each subject. Strictly, we excluded the participants in whom > 30 % of the variables were missing.

Our cohort included robust ($FI \leq 0.08$), pre-frail ($0.08 < FI < 0.25$) and frail ($FI \geq 0.25$) subjects (Song et al., 2010).

2.3. Plasma samples analysis

At recruitment, 6-h fasting blood samples were collected in Ethylenediaminetetraacetic acid (EDTA) tubes between 8 and 9 a.m. Within 1 h after blood draw, EDTA-blood was centrifuged at 1200 *g* for 15 min at room temperature to obtain platelet-free plasma, rapidly frozen and stored below − 80 °C, and thawed at the time of the assay.

Human Simple Plex assays (ProteinSimple, CA, USA) on Ella device (ProteinSimple, CA, USA) were used to quantify plasma concentration of interferon (IFN)-γ, IL-10, IL-6, TNF-α, IL-1β, TNF receptor 1 (TNFR1), TREM-1 and TREM-2 (sTREM-1, sTREM-2). Instrument calibration was performed using the incartridge factory standard curve, and plasma samples were measured with a dilution in Sample Diluent according to the manufacturer's instructions (ProteinSimple, CA, USA). A single well was used for each sample because triplicate assays are performed automatically in the Simple Plex assay microfluidic platform.

2.4. Statistical analysis

The statistical analyses were conducted using IBM SPSS Statistic software (version 27, IBM Inc., Chicago, IL, USA). The distribution of clinical and biological parameters was assessed using Kolmogorov-Smirnov test to investigate the adherence to the Gaussian graph. The normally distributed variables (age, BMI, MMSE and ADL scores) were reported as mean and standard deviation (SD), whereas non-normally distributed variables (FI, GDS score and marker concentrations) were expressed as median and interquartile range (IQR: 25–75th percentile). Percentages were used for categorical variables (i.e., sex and education), which were analyzed using Pearson's Chi-squared test. For the comparisons, the normally distributed data were analysed using the Student's t-test, whereas the non-normally distributed ones using the Kruskal-Wallis test and the Mann-Whitney U test. Multiple linear regressions were assessed to investigate the association between all the marker concentrations (dependent variable) and age, after adjustment for sex and a dichotomized FI variable (not frail vs. frail subjects). Values of $p < 0.05$ were considered statistically significant.

3. Results

The distribution of age in the overall cohort is shown in Fig. 1.

The main characteristics of the overall cohort (including centenarians and semi-supercentenarians) were reported in Table 1A, while the same characteristics in the subgroup of centenarians and semi-supercentenarians (people aged 105 and above) were reported in Table 1B.

Briefly, the mean age of the overall cohort (including centenarians

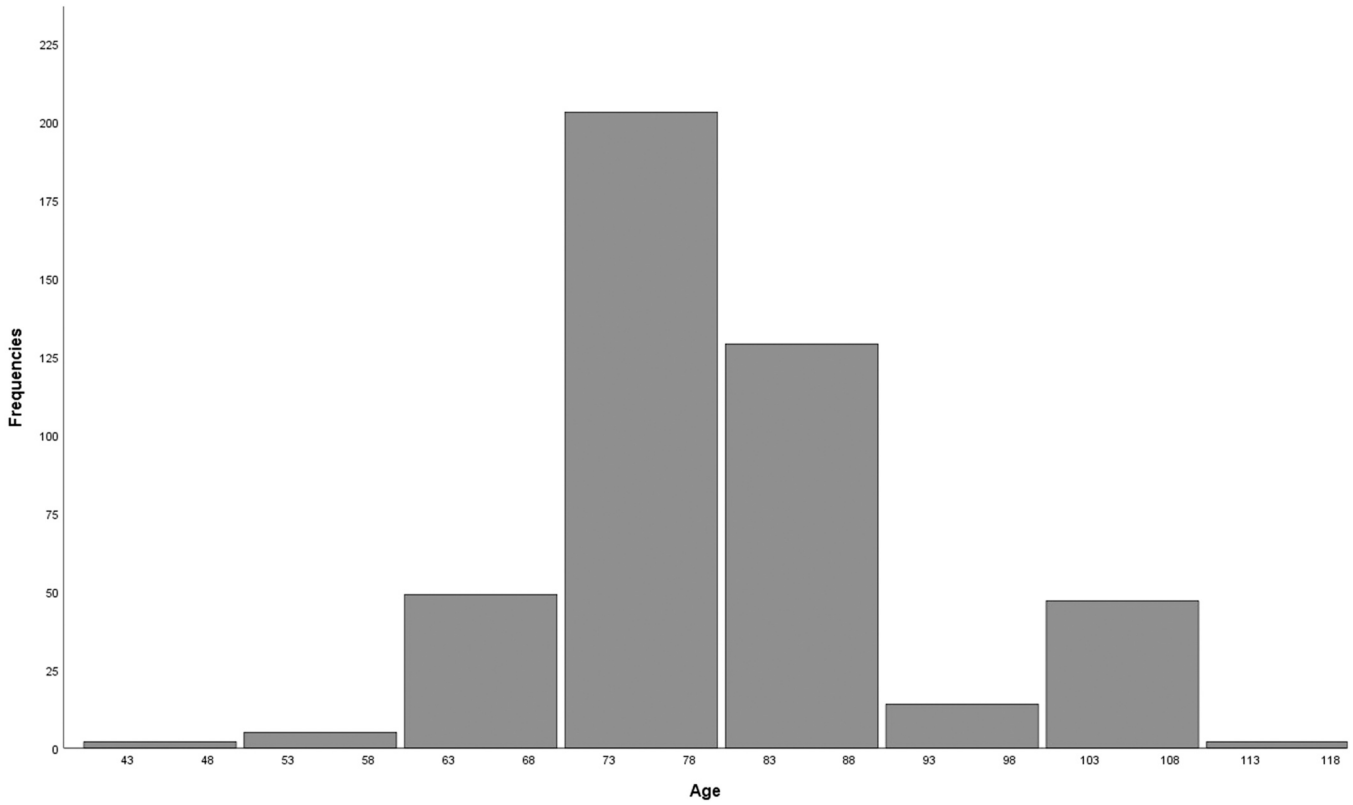

Fig. 1. Distribution of age in the overall cohort.

Table 1
Characteristics of the overall cohort (n = 452) (A) and of people aged 100 and above (n = 56) (B).

A	Variables	Overall cohort (n 452)
	Age (years)	79.7 (11.2)
	Sex (% women)	69.8 %
	FI	0.19 (0.12–0.29)
	BMI (kg/m^2)	24.6 (4.1)
	MMSE score	27.9 (3.5)
	ADL score	5.54 (0.70)
	GDS score	5.00 (2.00–9.00)
B	**Variables**	**People aged ≥ 100 (n 56)**
	Age (years)	103.3 (3.3)
	Sex (% women)	76.8 %
	FI	0.54 (0.48–0.60)
	BMI (kg/m^2)	21.4 (2.7)
	MMSE score	18.9 (7.6)
	ADL score	1.88 (1.78)
	GDS score	4.00 (1.50–9.50)

Age, BMI, MMSE and ADL scores were expressed as mean (standard deviation), whereas FI and GDS score as median (interquartile range). Sex distribution was reported as percentage of women.
FI, Frailty index; BMI: Body mass index; MMSE: Mini-mental state examination; ADL: Activities of daily living; GDS: Geriatric depression scale.

and semi-supercentenarians) was 79.7 (from 43 to 114) years, 69.8 % were women and the median FI value was 0.19 (IQR 0.12–0.29, from 0.00 to 0.75) (Table 1A). The mean BMI was 24.6 (SD 4.1). The MMSE had a mean score of 27.9 (SD 3.5) and the ADL scale of 5.54 (SD 0.70). The median GDS score was 5.00 (IQR 2.00–9.00) (Table 1A). In the overall cohort, 18.7 % of subjects received an education for 0–5 years, 28.6 % for 6–8 years, 31.4 % for 9–13 years and 21.3 % for more than 14 years.

The cohort included 36 centenarians and 20 semi-supercentenarians (i.e., persons aged 105 and above). In this subgroup, the mean age was 103.3 (from 100 to 114) years and 76.8 % were women (Table 1B). As expected, these people were more frail compared to the overall cohort (median FI value 0.54, IQR 0.48–0.60, from 0.28 to 0.75), had a lower BMI (21.4, SD 2.7) and were more functionally compromised (median ADL score 1.88, SD 1.78). Only 17 out of 56 centenarians completed the MMSE test and the mean score was 18.9 (SD 7.6). It is worth noting that, in some centenarians, the achieved score was influenced by the presence of physical deficits (e.g., visual and hearing deficits and hand arthritis) that affected the performance of the test. This subgroup had a GDS score of 4.00 (IQR 1.50–9.50) (Table 1B). Lastly, as expected, they were less educated; in fact, 50.0 % of these people received an education for 0–5 years, 18.8 % for 6–8 years, 15.6 % for 9–13 years and 15.6 % for more than 14 years.

The plasmatic concentrations of the inflammatory markers analyzed

Table 2
Plasmatic concentrations of the markers analyzed in the overall cohort (n = 452).

Variables	Values
IFN-γ (pg/mL)	0.72 (0.49–1.12)
IL-10 (pg/mL)	2.10 (1.58–2.88)
IL-6 (pg/mL)	2.92 (1.78–5.30)
IL-1β (pg/mL)	0.20 (0.11–0.35)
TNF-α (pg/mL)	9.87 (7.88–12.67)
TNFR1 (ng/mL)	1.42 (1.13–1.84)
sTREM-1 (ng/mL)	0.53 (0.40–0.72)
sTREM-2 (ng/mL)	37.38 (26.71–51.19)

Marker concentrations were expressed as median (interquartile range).
IFN-γ, Interferon- γ; IL-10, Interleukin-10; IL-6, Interleukin-6; IL-1β, Interleukin-1β; TNF-α, Tumour necrosis factor-α; TNFR1, Tumour necrosis factor receptor 1; sTREM, Soluble triggering receptor expressed on myeloid cells.

in the continuum of aging are reported in Table 2.

First, we compared the plasma concentrations of each marker analysed among robust (FI ≤ 0.08), pre-frail (0.08 < FI < 0.25) and frail individuals (FI ≥ 0.25) (12.6 %, 51.8 % and 35.6 % of the overall cohort, respectively). Marker concentrations were significantly higher in frail than in robust and pre-frail subjects, with TNFR1 also higher in pre-frail than robust subjects (Table 3).

Since no difference was found between robust and pre-frail individuals for all markers evaluated except TNFR1, we categorized subjects in not frail (FI < 0.25) and frail (FI ≥ 0.25). The not frail subjects (64.4 %) had a mean age of 76.1 (from 43 to 91) years, whereas the frail subjects had a mean age of 85.1 (from 58 to 114) years (Table 4).

Surprisingly, the frail group consisted of a higher percentage of men than the not frail group (39.0 % vs. 27.1 %, p = 0.02) (Table 4). Moreover, the not frail individuals were more educated (13.1 % received an education for 0–5 years, 30.3 % for 6–8 years, 34.4 % for 9–13 years and 22.1 % for more than 14 years) compared to the frail ones (30.3 % received an education for 0–5 years, 24.2 % for 6–8 years, 28.8 % for 9–13 years and 16.7 % for more than 14 years) (p < 0.001).

For each marker analysed, the plasma concentration was significantly higher in frail compared to not frail people (Table 4).

Table 5 provides the results obtained by means of the multiple linear regression analyses between the plasmatic concentrations of each marker (dependent variable) and sex, dichotomized FI (not frail vs. frail) and age (independent variables).

Briefly, the concentrations of most of the inflammatory markers analyzed increased significantly with chronological age after adjustment for sex and FI, except for IFN-γ, which was significantly affected only by FI. IL-10 and IL-1β concentrations were significantly associated only with chronological age, whereas the other markers were affected by all covariates (Table 5).

4. Discussion

The main result of our study is the different association found between the inflammatory components analyzed and chronological and/or biological age (frailty status).

Assuming that the phenomenon of inflammaging exists, and that chronological age is strongly associated with frailty, in our model the plasmatic concentration of IFN-γ was positively associated with frailty but not with age, while IL-10 and IL-1β only with chronological age. The other markers were associated with both aging and frailty. Another interesting finding of our study is that for the first time, we described an age-dependent increase in plasma levels of sTREM-1 and sTREM-2 and their significant association with frailty status.

During aging there are numerous phenotypic changes that occur in the components of both adaptive and innate immune responses (Fulop et al., 2023). These changes cause "inflammaging", a phenomenon which can be considered an adaptation or maladaptation able to change the trajectory of aging of each person (Fulop et al., 2023). In fact, the immune system reflects each person's exposure to stress throughout life (Franceschi et al., 2000b; Vitlic et al., 2014), just as frailty reflects increased vulnerability to stress and reduced homeostatic reserve (Clegg et al., 2013).

It should be mentioned that, as expected, we found that not frail people were younger and more educated than the frail ones.

Table 3
Plasmatic concentrations of the markers analyzed in people categorized in robust, pre-frail and frail.

Variables	Robust	Pre-frail	Frail	p
IFN-γ (pg/mL)	0.60 (0.45–0.86)	0.66 (0.44–0.95)	0.85 (0.54–1.72)[a]	**< 0.001**
IL-10 (pg/mL)	1.83 (1.32–2.25)	2.01 (1.56–2.47)	2.47 (1.74–3.67)[a]	**< 0.001**
IL-6 (pg/mL)	2.15 (1.32–3.12)	2.44 (1.62–3.78)	4.39 (2.59–7.82)[a]	**< 0.001**
IL-1β (pg/mL)	0.16 (0.11–0.24)	0.19 (0.11–0.29)	0.22 (0.11–0.40)	0.07
TNF-α (pg/mL)	8.07 (7.12–9.69)	8.91 (7.57–10.75)	11.70 (9.58–15.95)[a]	**< 0.001**
TNFR1 (ng/mL)	1.13 (1.00–1.45)	1.35 (1.11–1.63)[b]	1.76 (1.34–2.52)[a]	**< 0.001**
sTREM-1 (ng/mL)	0.48 (0.36–0.61)	0.47 (0.39–0.59)	0.67 (0.48–0.88)[a]	**< 0.001**
sTREM-2 (ng/mL)	30.60 (21.11–42.40)	32.97 (25.28–45.43)	44.59 (33.03–61.72)[a]	**< 0.001**

Marker concentrations were expressed as median (interquartile range).
[a] p < 0.001 vs. robust and pre-frail subjects; [b] p < 0.05 vs. robust subjects.
IFN-γ, Interferon- γ; IL-10, Interleukin-10; IL-6, Interleukin-6; IL-1β, Interleukin-1β; TNF-α, Tumour necrosis factor-α; TNFR1, Tumour necrosis factor receptor 1; sTREM, Soluble triggering receptor expressed on myeloid cells.

Table 4
Age, sex and plasmatic concentrations of the markers analyzed in people categorized in not frail and frail.

Variables	Not frail	Frail	p
Age (years)	76.1 (6.4)	85.1 (12.5)	**< 0.001**
Sex (% women)	72.9 %	61.0 %	**0.02**
IFN-γ (pg/mL)	0.64 (0.44–0.95)	0.85 (0.54–1.72)	**< 0.001**
IL-10 (pg/mL)	1.98 (1.51–2.46)	2.47 (1.74–3.67)	**< 0.001**
IL-6 (pg/mL)	2.30 (1.58–3.56)	4.39 (2.59–7.82)	**< 0.001**
IL-1β (pg/mL)	0.18 (0.11–0.28)	0.22 (0.11–0.40)	**0.04**
TNF-α (pg/mL)	8.83 (7.48–10.70)	11.70 (9.58–15.95)	**< 0.001**
TNFR1 (ng/mL)	1.31 (1.09–1.61)	1.76 (1.34–2.52)	**< 0.001**
sTREM-1 (ng/mL)	0.47 (0.39–0.59)	0.67 (0.48–0.88)	**< 0.001**
sTREM-2 (ng/mL)	32.80 (24.52–44.20)	44.59 (33.03–61.72)	**< 0.001**

Age was expressed as mean (standard deviation), whereas marker concentrations as median (interquartile range). Sex distribution was reported as percentage of women.
IFN-γ, Interferon- γ; IL-10, Interleukin-10; IL-6, Interleukin-6; IL-1β, Interleukin-1β; TNF-α, Tumour necrosis factor-α; TNFR1, Tumour necrosis factor receptor 1; sTREM, Soluble triggering receptor expressed on myeloid cells.

Table 5
Multiple linear regression model between each biomarker concentration as dependent variable and sex (reference category: men), dichotomized Frailty Index (FI) and age as independent variables.

	Covariates	R^2	B	SE	p
IFN-γ	Sex	0.06	-0.11	0.08	0.16
	FI		0.39	0.08	**< 0.001**
	Age		-0.00004	0.004	0.99
IL-10	Sex	0.11	0.09	0.05	0.11
	FI		0.08	0.06	0.19
	Age		0.01	0.003	**< 0.001**
IL-6	Sex	0.29	0.18	0.08	**0.02**
	FI		0.31	0.08	**< 0.001**
	Age		0.04	0.004	**< 0.001**
IL-1β	Sex	0.02	0.12	0.12	0.30
	FI		0.02	0.12	0.85
	Age		0.01	0.006	**0.02**
TNF-α	Sex	0.36	0.06	0.03	**0.05**
	FI		0.15	0.03	**< 0.001**
	Age		0.02	0.002	**< 0.001**
TNFR1	Sex	0.41	0.09	0.03	**0.005**
	FI		0.12	0.04	**0.001**
	Age		0.02	0.002	**< 0.001**
sTREM-1	Sex	0.24	0.12	0.04	**0.006**
	FI		0.10	0.05	**0.03**
	Age		0.02	0.002	**< 0.001**
sTREM-2	Sex	0.28	-0.12	0.04	**0.007**
	FI		0.15	0.05	**0.001**
	Age		0.02	0.002	**< 0.001**

R^2, coefficient of determination; B, unstandardized β coefficient; SE, standard error for the unstandardized β coefficient.
IFN-γ, Interferon-γ; IL-10, Interleukin-10; IL-6, Interleukin-6; IL-1β, Interleukin-1β; TNF-α, Tumour necrosis factor-α; TNFR1, Tumour necrosis factor receptor 1; sTREM, Soluble triggering receptor expressed on myeloid cells.

Surprisingly, the frail group consisted of a higher percentage of men than the not frail one, an apparent paradox already described in our previous study that included a portion of the subjects enrolled in the current research (Ferri et al., 2022).

In fact, our results contradict the so-called "male-female health-survival paradox," or "gender paradox," according to which women are longer-lived than men, although this survival advantage is linked to higher rates of disability and frailty during their lifetimes.

Interestingly, in our cohort, the frailty status (not frail vs. frail) seems to differently impact on inflammatory marker concentrations. Moreover, we found that IL-6, TNF-α and TNFR1 were positively associated (after all adjustments) with both chronological age and frailty. In linear regression analyses, the concentrations of these markers also appeared to be associated with sex. In fact, concentrations of the above markers were significantly higher in men than in women (data not shown).

The finding of the association with sex agrees with a recent study in which several associations between these inflammatory markers and frail were shown depending on sex (Searle et al., 2008).

These pro-inflammatory cytokines are increased sometimes to extraordinarily high levels in long-lived persons, but the consequences of this increment are very different from one individual to another (Baggio et al., 1998; Xia et al., 2016).

Generally, high serum levels of IL-6 correlate with many age-related chronic diseases (Fabbri et al., 2015), including cardiovascular, neurological and musculoskeletal diseases, as well as cancer and fatigue (Hiles et al., 2012). In the disease setting, increased concentrations of IL-6 (Collerton et al., 2012; Lai et al., 2014; Lee et al., 2016; Ma et al., 2018; Semmarath et al., 2019) and TNF-α (Collerton et al., 2012; Hubbard et al., 2009; Serviddio et al., 2009) play a key role in affecting metabolic signalling pathways, degrading muscle protein (Soysal et al., 2016), influencing endocrine systems and inducing nutritional dysregulation (Chen et al., 2014).

Interestingly, IL-6 and TNF-α levels showed a positive association with frailty computed by both the Fried's frailty phenotype model (Fried et al., 2001) and the FI model as described in this study and others (Tran Van Hoi et al., 2023; Niebla-Cárdenas et al., 2023).

The significant associations we found between TNFR1 concentration and both age and frailty, and the increase in TNFR1 concentrations already in the pre-frail state, further highlighted the importance of cell-to-cell communication in the aging process (Gonçalves et al., 2022), frailty and thus age-related diseases (Pansarasa et al., 2022).

Regarding the other pro-inflammatory components, IFN-γ concentration was significantly associated only with frailty, while IL-1β concentration only with age. The first result agrees with data obtained in another Italian cohort that showed a significant difference in the IFN-γ levels in frail vs. not frail 70-year-old women, whereas the second disagrees with the same study in which the authors described a positive correlation between frailty and IL-1β in women (Pansarasa et al., 2022).

Regarding IL-1β, in agreement with our results, most of the studies did not report significant association with frailty (Baylis et al., 2013; Qu et al., 2009), but mainly with increased risk of cognitive decline (e.g., AD) (Michaud et al., 2013; van den Biggelaar et al., 2007).

It should be noted that we cannot exclude that in our model the concentrations of these markers, in particular IFN-γ, were correlated with age anyway, but that these correlations were strongly mediated by frailty.

Finally, IL-10 concentration was found to be strongly associated with age and not with frailty. It is known that inflammation stimulates a corresponding increase in anti-inflammatory mediators to limit the damage that the inflammatory response might cause (Perretti and D'Acquisto, 2006; Franceschi, 2007). Consequently, the overstimulation of pro-inflammatory pathways along with an ineffective anti-inflammatory response could be a driving force in the development of frailty and age-related diseases (Morrisette-Thomas et al., 2014).

While numerous studies reported elevated IL-10 circulating levels in both old and very old people (Franceschi, 2007), the involvement of IL-10 in the etiopathogenesis of frailty has not yet been demonstrated. Indeed, it is likely that the effect of IL-10 on systemic inflammation is more critical in protecting older people from inflammation-associated diseases than substantially contributing to the diseases themselves and, thus, to frailty (Almanan et al., 2020).

Similarly, it could be assumed for IL-1β production. However, further studies are necessary to understand the mechanism(s) underlying the beneficial vs. pathologic effects of both IL-10 and IL-1β in aging and frailty.

The novelty of our study was the significant association described between circulating levels of sTREM-1 and sTREM-2 and age, sex and frailty. TREM receptors interact with toll-like receptors (TLRs) influencing the extent of inflammatory response (Arts et al., 2013; Klesney-Tait et al., 2006) and the production of inflammatory components by the activation of TREM-1 and the inhibition of TREM-2, respectively (Genua et al., 2014; Gibot, 2005). In addition to its expression in a cell membrane-bound form, both TREM-1 and TREM-2 are released as a soluble factor (sTREM-1 and sTREM-2).

TREM-1 acts by synergizing with TLRs to amplify the inflammatory responses to pathogens promoting sepsis-induced immune dysregulation and organ dysfunction (Bouchon et al., 2000; Boufenzer et al., 2021; Jolly et al., 2018). For these reasons, it is firstly linked with infection disease (Bouchon et al., 2001), but its beneficial effect is also recognized in the pathophysiology of non-infectious diseases (Tammaro et al., 2017; Gibot et al., 2004a, 2004b; Barraud and Gibot, 2011).

TREM-2 binds a variety of molecules such as bacterial products, DNA, lipoproteins, and phospholipids (Kober and Brett, 2017; Deczkowska et al., 2020). In the context of inflammation, TREM-2 is considered to behave oppositely to TREM-1 (Sharif and Knapp, 2008). Indeed, the induction of cellular phagocytic activity is a way to prevent the release of endogenous danger signals from dying cells (Deczkowska et al., 2020). Moreover, TREM-2 downstream signalling restricts inflammation by inducing the expression of anti-inflammatory genes (Deczkowska et al., 2020; Jaitin et al., 2019; Keren-Shaul et al., 2017).

Specifically, in the context of neuroinflammation, mutations in the TREM-2 gene are associated with risk of AD (Bellenguez et al., 2022; de Rojas et al., 2021). Furthermore, among the risk genes underlying sexual dimorphism in AD, a particular genetic profile of TREM-2 appears to induce altered microglial response in aged female tau mice (Zhu et al., 2021). In fact, in the regression analyses we also found a significant association between sTREM-1 and sTREM-2 and sex. The sTREM-1 concentrations were particularly higher in men than women (data not shown).

While different levels of gene expression in peripheral blood mononuclear cells from patients with mild cognitive impairment who later converted to AD have been described (Casati et al., 2018), as well as a lower plasma concentration of sTREM-2 in older patients with AD (Ferri et al., 2020), the association between TREMs levels and aging per se is poorly characterized (Henjum et al., 2016; Park et al., 2021; Fortin et al., 2007). To our knowledge still no studies have described associations between these molecules and frailty.

The main limitations of our study are its cross-sectional design and the possibility that our findings might reflect lifestyle factors other than the health determinants we have described and measured. While the role of the main potential variables (age, sex and frailty status) was considered in the analysis, residual confounding remains possible.

Finally, the main weakness of this study is the exclusion of all individuals with major chronic inflammatory diseases, although necessary to study the underlying mechanisms. In fact, it led to the exclusion of a portion of older people, distancing the results from real life and thus limiting their use in clinical practice.

Inflammaging is a widely described phenomenon, but the fine mechanisms that regulate the balance between inflammatory and anti-inflammatory markers as well as the interactions between the different components are not yet fully elucidated.

In conclusion, the characterization of an appropriate molecular

signature, e.g. through the computation of a biological frailty index (Sapp et al., 2023) based on these laboratory measures, may provide an adequate means to understand the complexity of the aging process and help to trace the trajectories of aging in relation to the health status of each subject, laying the foundation for personalized disease management.

Funding

This work was supported by the Italian Ministry of Health, under the Aging Network of Italian Research Hospitals (IRCCS), RCR-2022-23682286 (Ricerca Corrente Reti 2022).

CRediT authorship contribution statement

All authors contributed to Writing – review & editing. Conceptualization: B.A.; Methodology: B.A., E.F.; Formal analysis and Investigation: B.A., E.F.; Writing – original draft: B.A.; Writing – review & editing: B.A., D.M., E.T., G.V.; Funding acquisition: B.A., G.V., N.M.; Supervision: N. M.

Conflict of interest

The authors declare no competing interests.

Data Availability

Data will be made available on request.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mad.2023.111872.

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