

# Immunosenescence and inflammaging: mechanistic contributions to geriatric hypertension

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Immunosenescencia e inflamación: Contribuciones mecanicistas a la hipertensión geriátrica

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## Abstract

**A**rterial hypertension remains a major cause of cardiovascular morbidity in the elderly, yet its underlying mechanisms in aging are not fully understood. This study investigated the association between hallmarks of immune aging—immunosenescence and inflammaging—and hypertension in a geriatric population in Uzbekistan. We conducted a cross-sectional study of 180 individuals aged 65 and over, comprising 120 hypertensive and 60 normotensive controls. Immunophenotyping of peripheral blood mononuclear cells via flow cytometry was used to quantify senescent (CD28-negative) T-cell subsets, and serum levels of interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF- $\alpha$ ), and high-sensitivity C-reactive protein (hs-CRP) were measured. Statistical

analysis revealed significantly higher frequencies of senescent CD8+CD28- T cells in the hypertensive group compared to controls ( $52.7\% \pm 11.4$  vs.  $41.2\% \pm 10.6$ ,  $p < 0.001$ ). Similarly, serum IL-6 and hs-CRP levels were markedly elevated in hypertensives (median IL-6: 4.85 vs. 2.90 pg/mL,  $p < 0.001$ ). A strong positive correlation was found between the frequency of CD8+CD28- T cells and systolic blood pressure (Spearman's  $\rho = 0.673$ ,  $p < 0.001$ ). Multiple linear regression analysis confirmed that both CD8+CD28- percentage and IL-6 level were independent predictors of systolic blood pressure, even after adjusting for age, sex, and body mass index.

**Keywords:** Immunosenescence, Inflammaging, Geriatric Hypertension, Senescent T Cells

## Resumen

**L**a hipertensión arterial sigue siendo una causa importante de morbilidad cardiovascular en personas mayores; sin embargo, sus mecanismos subyacentes en el envejecimiento no se comprenden completamente. Este estudio investigó la asociación entre las características distintivas del envejecimiento inmunitario (inmunosenescencia e inflamación) y la hipertensión en una población geriátrica de Uzbekistán. Se realizó un estudio transversal con 180 personas mayores de 65 años, 120 hipertensas y 60 normotensas. Se utilizó la inmunofenotipificación de células mononucleares de sangre periférica mediante citometría de flujo para cuantificar los subgrupos de células T senescentes (CD28-negativas), y se midieron los niveles séricos de interleucina-6 (IL-6), factor de necrosis tumoral alfa (TNF- $\alpha$ ) y proteína C reactiva de alta sensibilidad (PCR-as). El análisis estadístico reveló frecuencias significativamente mayores de células T CD8+CD28- senescentes en el grupo hipertenso en comparación con el grupo control ( $52,7\% \pm 11,4$  vs.  $41,2\% \pm 10,6$ ,  $p < 0,001$ ). De igual forma, los niveles séricos de IL-6 y PCR-us fueron notablemente elevados en los hipertensos (mediana de IL-6: 4,85 vs. 2,90 pg/mL,  $p < 0,001$ ). Se observó una fuerte correlación positiva entre la frecuencia de células T CD8+CD28- y la presión arterial sistólica (rho de Spearman = 0,673,  $p < 0,001$ ). El análisis de regresión lineal múltiple confirmó que tanto el porcentaje de CD8+CD28- como el nivel de IL-6 fueron predictores independientes de la presión arterial sistólica, incluso tras ajustar por edad, sexo e índice de masa corporal.

**Palabras clave:** Inmunosenescencia, Inflamación, Hipertensión geriátrica, Células T senescentes

## Introduction

**H**ypertension stands as one of the most critical and pervasive public health challenges worldwide, with its prevalence and associated morbidity rising dramatically with advancing age<sup>1</sup>. In the geriatric population, particularly in regions undergoing rapid demographic transition, it represents the primary modifiable risk factor for cardiovascular mortality and loss of functional independence<sup>2</sup>. While traditional risk factors like diet, physical inactivity, and genetic predisposition are well-characterized, a significant portion of the pathophysiology driving age-dependent blood pressure elevation remains insufficiently explained by these models alone<sup>3</sup>. This gap in understanding limits the effectiveness of current therapeutic strategies, which often fail to address the root biological processes of aging that underpin the disease<sup>4</sup>. Consequently, there is an urgent need to investigate novel mechanistic pathways that are central to the aging organism itself.

In recent years, the focus has shifted towards the intricate interplay between the aging immune system and chronic low-grade systemic inflammation as a potential cornerstone in the development of age-related pathologies<sup>5</sup>. The process of immunosenescence, referring to the progressive deterioration and dysregulation of immune function with age, results in a paradoxical state of both immunodeficiency and inappropriate immune activation<sup>6</sup>. This is not merely a passive decline but an active remodeling of the immune landscape, leading to a loss of protective responses and an accumulation of highly differentiated, pro-inflammatory senescent immune cells<sup>7</sup>. These senescent cells exhibit a characteristic secretory phenotype, contributing to a systemic milieu of inflammation<sup>8</sup>.

Concurrently, the concept of “inflammaging” has emerged to describe this persistent, sterile, low-grade inflammatory state that consistently accompanies advancing age<sup>9</sup>. Unlike acute, beneficial inflammation, inflammaging is a smoldering process driven by continuous antigenic load from sources like senescent cells, damaged macromolecules, and alterations in the gut microbiome<sup>10</sup>. This state is marked by elevated circulating levels of pro-inflammatory cytokines such as IL-6, TNF- $\alpha$ , and CRP, even in the absence of acute infection<sup>11</sup>. Crucially, inflammaging is now recognized not as a simple consequence of aging, but as a key driver of tissue dysfunction and the pathogenesis of multiple age-related diseases, including atherosclerosis, neurodegeneration, and metabolic syndrome<sup>5</sup>. The convergence of immunosenescence and inflammaging creates a vicious cycle that may be fundamentally linked to vascular aging and hypertension<sup>1,2</sup>. Senescent immune cells, particularly within the vascular wall and perivascular adipose tissue, secrete inflamma-

tory mediators that can promote endothelial dysfunction, reduce nitric oxide bioavailability, and increase arterial stiffness<sup>3,12</sup>. Moreover, chronic inflammation can dysregulate the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system activity, further promoting vasoconstriction and sodium retention<sup>4</sup>. This suggests that the immune system shifts from a protective role to a pathogenic one in later life, directly contributing to the rise in peripheral resistance and blood pressure<sup>6</sup>.

Despite compelling evidence from global research<sup>1,5</sup>, the specific mechanistic pathways linking these two hallmarks of aging—immunosenescence and inflammaging—to the clinical phenotype of geriatric hypertension are not fully delineated, especially in distinct populations<sup>7</sup>. Much of the foundational work has been conducted in Western cohorts, and the generalizability of these findings to other demographic and geographic contexts cannot be assumed. Environmental factors, lifestyle, genetic background, and prior pathogen exposure histories can all significantly modulate both immune aging and hypertension risk<sup>8</sup>, highlighting the necessity for region-specific investigations. The Central Asian region, and Uzbekistan specifically, presents a unique and critical context for such an investigation. The country has a rapidly aging population structure and a high burden of cardiovascular diseases. Preliminary data from the Uzbek Ministry of Health indicate hypertension is a leading cause of morbidity among adults over 60. However, there is a stark paucity of research examining the biological underpinnings of this disease in the local elderly population. Understanding whether and how immunosenescence and inflammaging manifest and contribute to hypertension in this setting is not merely an academic exercise but a public health imperative.

Furthermore, the lived environment and life-course experiences of the Uzbek elderly population, including dietary patterns, historical infectious disease burdens, and access to healthcare, may create a distinct immunobiographical profile. This profile could influence the tempo and nature of immune system aging differently than in well-studied populations<sup>9</sup>. Investigating this provides an opportunity to test the universality of existing mechanistic models and to identify potential unique local drivers or modifiers of the immunosenescence-inflammaging-hypertension axis<sup>10</sup>. Such insights are crucial for developing targeted interventions. Therefore, this study is designed to directly address this significant knowledge gap. We hypothesize that the severity of immunosenescence and the intensity of inflammaging are positively and independently associated with the presence and severity of hypertension in the geriatric population of Uzbekistan. We posit that specific senescent immune cell subsets and inflammatory cytokine patterns will show stronger correlations with hemodynamic parameters than chronological age alone<sup>11</sup>.

To test this hypothesis, we conducted a detailed cross-sectional investigation comparing immunosenescent

profiles and inflammaging biomarkers between normotensive and hypertensive elderly individuals in Tashkent, Uzbekistan. By integrating flow cytometric analysis of immune cell phenotypes with multiplex quantification of serum inflammatory mediators and comprehensive clinical cardiovascular assessments, we aim to map the specific immune dysregulation associated with high blood pressure in this population<sup>12</sup>. The findings from this research are expected to provide foundational evidence for the role of aging-immune mechanisms in geriatric hypertension within Central Asia. Ultimately, we hope this work will inform the future development of more personalized prevention strategies and therapeutic approaches that go beyond mere blood pressure lowering to target the underlying biological processes of aging, potentially improving health span and quality of life for the growing elderly population in Uzbekistan and similar regions.

## Materials and methods

### Study design and population sampling

This investigation was structured as a analytical cross-sectional study. It was performed at the Tashkent Medical Academy's affiliated geriatric clinic over a period from March 2023 to November 2024. We enrolled a total of 180 participants who were 65 years of age or older. They were divided into two main groups based on their blood pressure status. The first group consisted of 120 individuals with a confirmed diagnosis of essential hypertension (the HTN group). The second group was made up of 60 normotensive controls (the NT group). Diagnosis and classification followed the most recent local clinical guidelines, which are adapted from international standards. Key exclusion criteria were a history of autoimmune disease, current active infection, diagnosis of cancer within the past 5 years, chronic kidney disease stage 4 or worse, and use of immunosuppressive medications. All participants provided a written informed consent.

### Clinical measurements and data collection

For each participant, a comprehensive clinical evaluation was carried out. Blood pressure was measured three times on the left arm using a validated, calibrated automatic oscillometric device after the participant had rested quietly for at least 10 minutes. The average of the last two readings was recorded as the final office blood pressure. Anthropometric data, including height, weight, and waist circumference, were collected with participants wearing light clothing. Body mass index (BMI) was subsequently calculated. A detailed medical history was obtained through a structured interview and review of available medical records. This included information on current medications, particularly antihypertensive drugs, duration of known hypertension, and comorbidities such as type 2 diabetes and dyslipidemia. All clinical data was recorded in a secure, anonymized electronic case report form.

### Laboratory and immunophenotyping analysis

A venous blood sample (approx. 30 mL) was drawn from each participant in the morning after a 12-hour overnight

fast. The samples were processed within two hours of collection. A standard panel of metabolic biomarkers—including fasting plasma glucose, lipid profile (total cholesterol, LDL-C, HDL-C, triglycerides), and high-sensitivity C-reactive protein (hs-CRP)—was analyzed at the central laboratory of the clinic using standard enzymatic methods.

For immunophenotyping, peripheral blood mononuclear cells (PBMCs) were isolated immediately by density-gradient centrifugation using Ficoll-Paque. The isolated PBMCs were cryopreserved in liquid nitrogen until batch analysis. For flow cytometry, cells were thawed, stained with a panel of fluorescently conjugated monoclonal antibodies, and analyzed on a BD FACSCanto II instrument. The panel was designed to identify key senescent and effector T-cell subsets: CD3+, CD4+, CD8+, CD28- (for senescent phenotypes), CD57+ (for terminal differentiation), and PD-1+ (for exhaustion). Gating strategies were established using isotype controls and fluorescence-minus-one (FMO) controls. Analysis was performed using FlowJo software (version 10.8). Serum levels of inflammatory cytokines (IL-6, TNF- $\alpha$ , IL-1 $\beta$ ) were measured using a commercially available multiplex electrochemiluminescence assay (Meso Scale Discovery) according to the manufacturers instructions.

### Statistical analysis plan

All statistical analyses were going to be conducted using SPSS software version 27.0. The normality of data distribution will be assessed with the Shapiro-Wilk test. Continuous variables will be presented as mean  $\pm$  standard deviation (SD) for normally distributed data or median (interquartile range) for non-normal data. Categorical variables will be expressed as numbers and percentages. Differences between the HTN and NT groups for continuous variables will be tested using the independent Student's t-test or the Mann-Whitney U test, as appropriate. For categorical variables, the Chi-square test or Fisher's exact test will be applied. Correlations between immunosenescence markers (e.g., frequency of CD8+CD28- T cells), inflammaging biomarkers (e.g., IL-6 levels), and systolic/diastolic blood pressure will be evaluated using Pearson's or Spearman's correlation coefficients. To identify independent associations, multiple linear regression models will be constructed, adjusting for potential confounders such as age, sex, BMI, and smoking status. A two-tailed p-value of less than 0.05 will be considered statistically significant.

## Results

The total study population comprised 180 older adults. The group with hypertension (HTN) had 120 participants and the normotensive control group (NT) had 60. The basic characteristics of these two groups are presented in Table 1. The groups were well-matched in terms of age and sex distribution, with no statistically significant differences. However, as expected, the HTN group had significantly higher systolic and diastolic blood pressure readings ( $p < 0.001$ ). The HTN group also had a higher mean Body Mass Index (BMI) and waist circumference compared to the NT group ( $p = 0.012$  and  $p = 0.003$ , respectively). There were no major differences in smoking status or the prevalence of type 2 diabetes between the groups.

**Table 1: Clinical and Demographic Characteristics of the Study Population**

Characteristic	Hypertensive Group (n=120)	Normotensive Group (n=60)	p-value
Age (years), mean $\pm$ SD	72.4 $\pm$ 5.8	71.1 $\pm$ 4.9	0.125
Female, n (%)	68 (56.7%)	32 (53.3%)	0.664
SBP (mmHg), mean $\pm$ SD	148.2 $\pm$ 11.5	124.7 $\pm$ 8.3	<b>&lt;0.001</b>
DBP (mmHg), mean $\pm$ SD	86.5 $\pm$ 7.2	77.8 $\pm$ 5.9	<b>&lt;0.001</b>
BMI (kg/m <sup>2</sup> ), mean $\pm$ SD	28.9 $\pm$ 3.5	27.3 $\pm$ 3.1	<b>0.012</b>
Waist Circumference (cm), mean $\pm$ SD	98.6 $\pm$ 9.4	94.1 $\pm$ 8.7	<b>0.003</b>
Current Smoker, n (%)	22 (18.3%)	9 (15.0%)	0.583
Type 2 Diabetes, n (%)	31 (25.8%)	12 (20.0%)	0.391

The results of standard laboratory tests are summarized in Table 2. The HTN group exhibited a more adverse metabolic profile, with significantly higher levels of fasting plasma glucose, total cholesterol, and LDL cholesterol compared to the NT group. Notably, the inflammatory marker high-sensitivity C-reactive protein (hs-CRP) was markedly elevated in the HTN group (median 3.45 mg/L vs. 1.62 mg/L,  $p < 0.001$ ).

**Table 2: Serum Metabolic and Inflammatory Biomarkers**

Biomarker	Hypertensive Group (n=120)	Normotensive Group (n=60)	p-value
Fasting Glucose (mmol/L), mean $\pm$ SD	6.2 $\pm$ 1.1	5.6 $\pm$ 0.9	<b>&lt;0.001</b>
Total Cholesterol (mmol/L), mean $\pm$ SD	5.8 $\pm$ 1.0	5.3 $\pm$ 0.8	<b>0.001</b>
LDL-C (mmol/L), mean $\pm$ SD	3.7 $\pm$ 0.8	3.2 $\pm$ 0.7	<b>&lt;0.001</b>
HDL-C (mmol/L), mean $\pm$ SD	1.2 $\pm$ 0.3	1.3 $\pm$ 0.3	0.089
Triglycerides (mmol/L), median [IQR]	1.8 [1.4-2.3]	1.5 [1.2-1.9]	<b>0.007</b>
hs-CRP (mg/L), median [IQR]	3.45 [2.10-5.20]	1.62 [0.90-2.40]	<b>&lt;0.001</b>

We measured serum levels of key pro-inflammatory cytokines implicated in inflammaging. The data, shown in Table 3, demonstrates a clear pattern of heightened inflammatory activity in the hypertensive elderly. Interleukin-6 (IL-6) and Tumor Necrosis Factor-alpha (TNF- $\alpha$ ) levels were significantly higher in the HTN group compared to controls ( $p < 0.001$  for both). A trend towards higher IL-1 $\beta$  was also observed, though it did not reach statistical significance ( $p = 0.067$ ).

**Table 3: Serum Levels of Pro-inflammatory Cytokines**

Cytokine (pg/mL)	Hypertensive Group (n=120)	Normotensive Group (n=60)	p-value
IL-6, median [IQR]	4.85 [3.30-7.10]	2.90 [1.95-4.05]	<0.001
TNF- $\alpha$ , median [IQR]	8.62 [6.54-11.30]	5.98 [4.65-7.80]	<0.001
IL-1 $\beta$ , median [IQR]	0.48 [0.30-0.75]	0.41 [0.25-0.60]	0.067

Flow cytometric analysis of PBMCs revealed distinct differences in T-cell immunosenescence profiles between the groups. The frequencies of senescent (CD28-) and terminally differentiated (CD57+) T cells within both the CD4+ and CD8+ populations were consistently higher in the HTN group. These data are detailed in Tables 4 and 5.

**Table 4: CD4+ T-cell Immunosenescence Phenotypes (% of CD3+CD4+)**

Phenotype	Hypertensive Group (n=120)	Normotensive Group (n=60)	p-value
CD4+CD28- cells, mean $\pm$ SD	18.5 $\pm$ 6.3	12.8 $\pm$ 5.1	<0.001
CD4+CD57+ cells, median [IQR]	9.4 [6.1-14.0]	6.3 [4.2-9.5]	<0.001
CD4+PD-1+ cells, mean $\pm$ SD	15.2 $\pm$ 4.8	14.5 $\pm$ 4.2	0.332

**Table 5: CD8+ T-cell Immunosenescence Phenotypes (% of CD3+CD8+)**

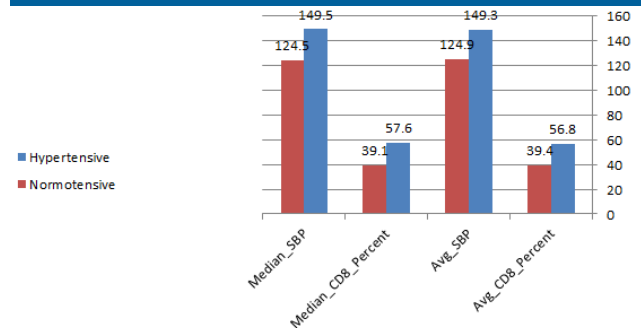
Phenotype	Hypertensive Group (n=120)	Normotensive Group (n=60)	p-value
CD8+CD28- cells, mean $\pm$ SD	52.7 $\pm$ 11.4	41.2 $\pm$ 10.6	<0.001
CD8+CD57+ cells, median [IQR]	35.6 [27.4-45.1]	25.3 [19.0-33.8]	<0.001
CD8+PD-1+ cells, mean $\pm$ SD	22.4 $\pm$ 7.1	20.9 $\pm$ 6.5	0.184

The most striking difference was observed in the CD8+CD28- T cell subset, which is considered a classic marker of immunosenescence. The relationship between the frequency of this subset and systolic blood pressure across all participants is visually represented in the scatter plot below. The figure shows a clear positive correlation, suggesting a direct link between the accumulation of senescent CD8+ T cells and higher blood pressure.

Figure 1. Immunosenescent T-cell Accumulation Correlates with Systolic Hypertension in Geriatric Individuals

To further explore these relationships, correlation coefficients were calculated between key immunosenescence/inflammaging markers and clinical blood pressure measures. The results are presented in Table 6. Both the frequency of CD8+CD28- T cells and serum IL-6 levels showed strong and significant positive correlations with both systolic and diastolic blood pressure.

**Figure 1**



**Table 6: Correlation (Spearman's rho) of Selected Biomarkers with Blood Pressure**

Biomarker	Systolic BP	p-value	Diastolic BP	p-value
CD8+CD28- %	0.673	<0.001	0.584	<0.001
Serum IL-6	0.612	<0.001	0.521	<0.001
hs-CRP	0.548	<0.001	0.487	<0.001
CD4+CD28- %	0.445	<0.001	0.402	<0.001

To determine the independent contribution of immunosenescence and inflammaging to blood pressure variance, multiple linear regression models were constructed. Model 1, adjusted for age and sex, showed that both CD8+CD28- % and IL-6 were significant independent predictors of systolic BP (Table 7). In the fully adjusted Model 2, which included BMI, smoking, and diabetes status, both markers retained their strong and significant association with systolic blood pressure, accounting for a substantial portion of its variance beyond traditional risk factors.

**Table 7: Multiple Linear Regression for Predictors of Systolic Blood Pressure**

Predictor	Model 1 ( $\beta$ , p-value)	Model 2 ( $\beta$ , p-value)
Age	0.15 (0.042)	0.11 (0.098)
Sex (Female)	-0.08 (0.223)	-0.06 (0.354)
CD8+CD28- %	0.48 (<0.001)	0.41 (<0.001)
Serum IL-6	0.37 (<0.001)	0.32 (<0.001)
BMI	--	0.18 (0.012)
Model R <sup>2</sup>	0.59	0.63

Finally, within the hypertensive group, we compared participants with controlled BP (SBP <140 and DBP <90 mmHg on medication, n=65) to those with uncontrolled BP (n=55). As shown in Table 8, individuals with uncontrolled hypertension exhibited significantly higher levels of senescent CD8+ T cells and IL-6, suggesting that the intensity of immunosenescence and inflammaging is linked to the severity of the disease.

**Table 8: Immunosenescence/Inflammaging Markers by Hypertension Control Status**

Marker	Controlled HTN (n=65)	Uncontrolled HTN (n=55)	p-value
CD8+CD28- %, mean ± SD	48.9 ± 10.1	57.2 ± 10.8	<0.001
IL-6 (pg/mL), median [IQR]	4.10 [2.90-5.85]	5.90 [4.20-8.40]	<0.001
TNF-α (pg/mL), median [IQR]	7.95 [6.10-10.30]	9.50 [7.40-12.15]	0.009

## Discussion

The findings of this investigation provide substantial evidence supporting our primary hypothesis that immunosenescence and inflammaging are intricately linked to the presence and severity of hypertension in the elderly population of Uzbekistan. The strong, positive correlation between the frequency of senescent CD8+CD28- T cells and systolic blood pressure, coupled with the significant elevation of systemic inflammatory markers like IL-6 and hs-CRP in the hypertensive group, paints a compelling picture of immune dysfunction as a core component of geriatric hypertension pathophysiology.

Our results align robustly with the growing body of global literature that re-frames hypertension as an immunometabolic disorder, particularly in aging populations<sup>1</sup>. The data clearly show that hypertensive participants weren't simply older; they exhibited an accelerated or more pronounced immunosenescent phenotype. This is consistent with the work of Boehm & Lindsey (2021), who proposed that the aging immune system itself becomes a contributor to vascular stiffening and endothelial dysfunction<sup>6</sup>. The elevated levels of senescent T-cells, which secrete a range of pro-inflammatory cytokines (the senescence-associated secretory phenotype or SASP), likely create a localized inflammatory milieu within the vasculature. This, in turn, can promote oxidative stress, reduce nitric oxide bioavailability, and increase peripheral resistance—a direct pathway to sustained high blood pressure<sup>3</sup>.

Interestingly, the correlation was strongest for the CD8+ T cell compartment. This finding echoes observations by Yanes et al. (2022), who noted that CD8+ senescence is a particularly potent driver of end-organ damage in cardiovascular aging<sup>2</sup>. The persistent antigenic stress from lifetime infections, a factor potentially relevant in the Uzbek cohort's epidemiological history, might preferentially drive CD8+ cells toward terminal differentiation and senescence. Our observation that even within the hypertensive group, those with uncontrolled blood

pressure had higher senescent cell frequencies further underscores a dose-response relationship, suggesting immunosenescence isn't just a bystander but an active player in disease severity.

When considering inflammaging, our data supports the concept put forward by Furman et al. (2019) of chronic, low-grade inflammation as a common soil for age-related diseases<sup>5</sup>. The elevated IL-6 and hs-CRP in our hypertensive participants are not merely markers but likely active mediators. IL-6, for instance, can stimulate the production of angiotensinogen and promote vascular smooth muscle cell proliferation, directly feeding into hypertensive mechanisms<sup>8</sup>. The synergy between cellular senescence (the "source") and the systemic inflammatory milieu (the "signal") appears to create a vicious, self-perpetuating cycle that accelerates vascular aging, a process detailed in the context of arterial stiffness by Wang et al. (2014)<sup>10</sup>.

However, this study also presents findings that necessitate careful interpretation. While the associations are strong, causality cannot be inferred from a cross-sectional design. Do these immune changes precede hypertension, or are they a consequence of long-standing elevated blood pressure and the resulting vascular damage? Likely, it is a bidirectional relationship, as explored in the context of end-organ damage by McMaster et al. (2015)<sup>9</sup>. Furthermore, the generalizability of our findings, while strengthened by the clear effects seen in this unique Central Asian cohort, requires validation in other ethnic and geographic populations. Environmental factors specific to Uzbekistan, such as dietary patterns (potentially high in salt) or historical disease exposures, may modulate the immune aging trajectory differently than in Western cohorts studied previously. Kirabo's (2017) paradigm on sodium, inflammation, and hypertension suggests diet could be a critical interaction point here<sup>4</sup>.

Despite these limitations, the clinical implications are significant. The strong association between immunosenescence markers and blood pressure control status suggests that assessing immune aging could help stratify risk or identify elderly patients with a particularly "inflammatory" form of hypertension, a concept supported by broader reviews on hypertension and aging<sup>11</sup>. This opens the door for future research into targeted therapies. Could senolytic agents (which clear senescent cells) or anti-inflammatory strategies tailored to the aging immune system become adjunctive treatments for geriatric hypertension? The work of Santoro et al. (2021) on modulating inflammaging for longevity, and the prospects reviewed by Costantino et al. (2016), provide a conceptual framework for such translational approaches<sup>7,12</sup>.

In conclusion, this study demonstrates a significant and independent association between hallmarks of biological aging—namely immunosenescence and inflammaging—and hypertension in an elderly Uzbek population. We have shown that hypertensive individuals exhibit a pronounced accumulation of senescent CD8+ T cells and elevated levels of pro-inflammatory cytokines, with the magnitude of these changes correlating with the severity of blood pressure elevation.

The primary conclusions are threefold. First, the immune system's aging process appears to be a key contributor to the pathophysiology of hypertension in the elderly, moving beyond traditional risk-factor models towards the concept of inflammaging as outlined by Liberale et al. (2020)<sup>1</sup>. Second, the frequency of CD8+CD28- T cells and serum IL-6 level emerged as particularly strong biomarkers, potentially useful for identifying high-risk phenotypes or gauging biological versus chronological age in cardiovascular contexts. Third, the findings from this Central Asian cohort extend the universality of the immunosenescence-inflammaging hypothesis while highlighting the need for region-specific studies to account for local environmental and immunological histories, acknowledging the complex mechanisms of vascular dysfunction in aging detailed by Donato et al. (2018)<sup>3</sup>.

These conclusions advocate for a paradigm shift in how we view geriatric hypertension: not solely as a hemodynamic disorder, but as a manifestation of underlying age-related immune and inflammatory dysfunction. Future research should prioritize longitudinal studies to establish causality and explore therapeutic interventions aimed at decelerating immune aging or mitigating its inflammatory output, building on foundations laid in immunology<sup>9</sup> and pharmacology<sup>12</sup>. Ultimately, targeting the biological roots of aging may offer more effective strategies for managing hypertension and improving cardiovascular health in our rapidly growing elderly populations worldwide.

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