Ageing and immunity: unraveling the association between immunosenescence and frailty

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General introduction

GENERAL INTRODUCTION

People are living longer worldwide, leading to an unprecedented increase in the ageing population (1). By 2030, one out of every six individuals will be 60 years or older. The proportion of the population aged 60 years or older is expected to increase from 1 billion in 2020 to 1.4 billion by 2030. The global population of those aged 60 years and above will double by 2050, reaching 2.1 billion (1). The global population aged over 65 is growing more rapidly than any other age group (1, 2). As a result of this demographic shift, it is essential to explore strategies that enhance the quality of life of older adults and enable them to live independently (2).

Healthy ageing and biological age

In later life, chronic diseases become increasingly common, with most older adults experiencing one or more conditions (3). In countries where life expectancy is highest, the prevalence of chronic disease and disability is also greater (4). This suggests that a longer lifespan does not necessarily translate into a healthier life, but is often accompanied by a greater burden of disease.

While the risk of health problems increases with age, their manifestations are highly heterogeneous among older individuals. Some people over 70 may present with multiple comorbidities and frailty, whereas others remain healthy, physically active, and capable of independent living. Such variability is influenced by a wide range of factors, including lifestyle, environmental exposures, socioeconomic status, (epi) genetic predispositions, and encounters with infectious agents.

Given this heterogeneity, there is increasing recognition that chronological age alone is an insufficient variable to understand older individuals' health status. Instead, biological age provides a more accurate reflection of the ageing process, as it incorporates diverse physiological, molecular, and clinical factors. Biological age captures how an individual is actually ageing, beyond what is indicated by the calendar, thereby helping to explain the wide variability in health outcomes observed in later life. Frailty has emerged as a key concept in this context. Measuring frailty offers a practical means of identifying individuals who are most vulnerable to adverse outcomes and in need of targeted interventions and/or treatment. Classifying people according to frailty status enables a more accurate classification of health, supporting the delivery of more tailored and effective care within an ageing and heterogeneous population.

Frailty

Frailty, which is highly prevalent and observed in 20% to 30% of the older population over 75 years (5), is a clinical state characterized by a decline in functioning across

multiple physiological systems, accompanied by increased vulnerability to stressors, which results in high risk of poor health outcomes, including falls, incident disability, hospitalization and mortality (6). Frailty has been shown to significantly elevate the risk of adverse outcomes of infectious diseases such as COVID-19 in older individuals. Consequently, it is crucial to elucidate which mechanisms may underlie the increased susceptibility to adverse outcomes to chronic and infectious disease in older patients with frailty.

There are many approaches to identifying frailty. Frailty may present as physical or psychological, or a combination of both (7). Common definitions of physical frailty include a specific phenotype model constructed from five components developed by Fried, comprising exhaustion, unintentional weight loss, low muscle strength, slow walking speed, and low physical activity, which is used as a dichotomous scale where individuals are categorized as frail or not based on specific criteria thresholds (6). Although a number of frailty definitions have been developed, Fried et al's description of the frailty phenotype remains the reference frame in geriatric medicine. Studies have demonstrated that the frailty phenotype was associated with negative health outcomes, including mortality and morbidity (8). However, there are no standardized definitions of how frailty should be measured, and studies use many different methods to measure and define frailty generally. A commonly used tool is the Clinical Frailty Scale (CFS), with a continuous scoring system, enhancing its utility in clinical settings by enabling the quantification of frailty along a spectrum rather than as a binary state. Moreover, the CFS is well-validated and has been used in various settings (9).

Immunosenescence and frailty

It has been well established that the immune system becomes compromised with age and is further altered with frailty. Age-related changes occur in both arms of immunity, innate and adaptive, a phenomenon collectively known as immune senescence (10). Studies have revealed this phenomenon to result in an increased frequency and severity of infection, as well as in lower immune surveillance of malignant cells, a reduced discrimination between self and non-self, and a decreased efficacy of vaccination in older individuals (11, 12).

The innate immune system, serving as the primary defense mechanism against injuries and infections, provides an immediate reaction to external stressors. It plays a crucial role in shaping immune responses against infections and inducing inflammation. The innate immunity is an antigen-independent (non-specific) defense system that is triggered when a pathogen intrudes (13). The rapid recruitment of immune cells occurs through the production of cytokines and chemokines. Cytokine production

during innate immunity induces many defense mechanisms while also activating local cellular responses to infection or injury, through the mobilization and activation of antigen-presenting cells (APCs). Dysregulation of the inflammatory cytokines results in a state of chronic, low-grade, sterile inflammation, also called inflammageing, which is often associated with chronic inflammatory or autoimmune diseases. In addition, ageing affects key cellular functions of macrophages, neutrophils, and natural killer cells, reducing their phagocytic and cytotoxic activities (14, 15). This diminished capacity not only slows the initial immune response to pathogens but also affects the regulation of inflammatory processes. Inflammageing is also thought to be triggered both by the age-related declines in the adaptive immune system (as a compensatory response), as well as by the age-related accumulation of (immune-reactive) debris (11).

Unlike the components of the innate immune system that are present before the onset of infection, in adaptive immunity, the immune response is triggered by antigen recognition and results in the formation of memory cells (16). The adaptive immunity is critical when innate immunity is insufficient in eliminating infectious agents. It is based on the recognition of “non-self” antigens, inducing pathogen-specific immunologic effector pathways that eliminate specific pathogens. This process results in the development of an immunologic memory that can eliminate a specific pathogen rapidly upon subsequent infections. The cells of the adaptive immune system include antigen-specific T cells, which are activated to proliferate through the action of APCs, and B cells, which produce antibodies. The function and regulation of adaptive immunity rely on the interaction between fully matured dendritic cells, T cells, cytokines, and various signaling molecules (10).

Immunosenescence reflects age-related changes in the innate and adaptive immune system. The adaptive immune response is notably compromised due to thymic atrophy that occurs with increasing age. The thymus is critical for the maturation of T-cells, and its diminished function results in a reduced output of naïve T-cells. This leads to a decreased diversity in the T-cell receptor repertoire, impairing the body’s ability to respond to new antigens (17). Moreover, the existing T-cells often exhibit a phenomenon known as replicative senescence, whereby repeated stimulation causes them to lose their proliferative capacity and enter a state of functional exhaustion. The B-cell lineage also undergoes significant alterations with age. There is a shift in B-cell subsets, with a noticeable decrease in naïve B-cells and an increase in memory B-cells. Consequently, older adults often show a poorer response to new infections and vaccines, and a higher prevalence of autoantibody production (18).

The relationship between frailty and the phenomena of immunosenescence and inflammageing remains a significant area of research, with many aspects still unclear.

While ageing influences the immune system, leading to both phenotypical and functional changes, how these alterations specifically contribute to the development of frailty is not well-defined. The intersection of these processes is crucial for understanding why some individuals age more successfully than others and what role the immune system plays in this divergence. Despite the recognized link between a declining immunity and increased vulnerability to age-related diseases, the direct pathways connecting immunosenescence and inflammageing to the physiological state of frailty have yet to be fully elucidated. Addressing these knowledge gaps is essential not only for advancing therapeutic strategies to enhance healthy ageing and reducing frailty-related complications but also for guiding treatment decisions, as frail patients may respond differently to therapies in terms of both effectiveness and risk of side effects.

The role of immunosenescence and frailty in COVID-19 and cancer

This thesis focuses on two significant diseases of modern times: COVID-19 and cancer, both of which are highly influenced by the age-related immune decline.

The COVID-19 pandemic has disproportionately affected older adults, who not only face heightened susceptibility to SARS-CoV-2 but also exhibit reduced vaccine responsiveness (19-21). Previous studies discussed immunosenescence and inflammageing as key factors influencing vulnerability to novel pathogens such as the SARS-CoV-2 virus (22, 23), highlighting the critical interplay between age-related frailty and the body's inflammatory response to the virus.

This reduced immune responsiveness is particularly problematic in older individuals who face higher mortality rates. The severe disease progressions and poorer outcomes observed in the ageing population underscore the need for research into how ageing-related changes in the immune system and frailty contribute to the severity of infections like COVID-19.

Among chronic diseases, cancer remains one of the principal causes of death in older populations. In cancer, the relationship between immunosenescence and disease progression is similarly critical. The ageing immune system not only becomes less efficient at surveilling and eliminating cancer cells but may also respond less effectively to cancer treatments that rely on immune activation (24). Moreover, processes related to defective wound repair may trigger carcinogenesis (25). Immunosenescence may thus compromise the effectiveness of these therapies, which are designed to harness the body's immune response to target and kill cancer cells.

Aim of this thesis

The overall aim of this thesis is to uncover how age-related changes in the immune system are associated with frailty and disease outcomes of two prevalent health challenge paradigms: cancer (more specifically, melanoma) and COVID-19. These conditions are particularly relevant as they represent significant health challenges in the older population, cancer being the leading cause of death, and COVID-19 exemplifying the high vulnerability of older adults to infectious diseases. This exploration is important for developing targeted interventions that could improve the quality of life in older patients.

Study populations

To address our research question within the COVID-19 paradigm, we used data from three cohorts in the Netherlands: COVID-OLD, COVID-Predict and CliniCo.

The **COVID-OLD study** is a retrospective multicenter cohort study that included patients aged 70 years and older who were hospitalized with COVID-19 from 27 February to 14 May 2020 in the Netherlands. Data were collected from 19 Dutch hospitals. The **Covid-Predict study** is a consortium of hospitals that aims to understand and predict COVID-19-related outcomes and to evaluate treatment options. Data were collected from 9 Dutch hospitals. The **CliniCo study** is a multicenter prospective cohort study that aims to describe clinical characteristics, disease course, and outcome of patients with COVID-19 and aims to develop diagnostic and prognostic prediction models for COVID-19. Data were collected from 6 Dutch hospitals.

To address our research questions within the cancer paradigm, we first used the prospective tumor-specific **T-Cell IMMunity in patients with solid tumors study** (TCIMM study). This prospective observational cohort study aimed to understand the immune factors related to the efficacy and side effects of immunotherapy in treated cancer patients by performing an in-depth analysis of systemic and intra-tumoral immune parameters using blood, tumor, intestinal and faecal samples.

Finally, we used three ongoing studies: 1) **The Triage of Elderly Needing Treatment study** (TENT study), 2) **IMmunotherapy in AGINg patiEnts study** (IMAGINE study), and 3) **The Tolerability and safety of immunotherapy study** (ImToSa study).

The **TENT study** is a prospective study. Patients who were candidates for intensive treatments (chemotherapy, (chemo-)radiation therapy, or major surgery) underwent frailty screening based on the Geriatric 8 (G-8) questionnaire and the Six-Item Cognitive Impairment Test (6CIT). If screening revealed potential frailty, a conventional geriatric assessment was performed. The study aimed to investigate

associations between geriatric characteristics and outcomes of treatment that are relevant to older patients.

The **IMAGINE study** is a prospective cohort study in patients who were treated in the LUMC with immunotherapy. Outcomes, including toxicity and hospitalization, were prospectively registered from medical charts.

The **ImToSa study** is a partly retrospective cohort study; some patients were included after treatment, and others before treatment. All patients treated with immunotherapy were included in our study population. The initial aim of the study was to assess age-related differences in side-effects and predictors of toxicity, including sex, geriatric characteristics, and previous treatments.

Outline of this thesis

Ageing is associated with several physiological changes, including changes in the immune system. Age-related changes in the innate and adaptive immune system are thought to contribute to frailty. In **Chapter 2**, a systematic review of current literature was conducted to scope current understanding of the immunological determinants of frailty, potentially leading to the development and delivery of more effective care for older individuals.

During the COVID-19 pandemic, older hospitalized patients faced a significant mortality risk, emphasizing the importance of understanding the interplay between frailty and inflammatory response to the SARS-CoV-2 virus. In **Chapter 3**, the association of frailty with inflammatory markers and its role in the relationship between inflammatory markers and in-hospital mortality among older patients hospitalized for COVID-19 was investigated.

Immunotherapy with checkpoint inhibition (ICI) is increasingly prescribed in older patients with cancer. High age, especially in combination with frailty, has been associated with immune senescence, thereby possibly hindering ICI effectiveness. In **Chapter 4**, the association between blood cell immune senescence markers and age, frailty and response to anti-PD-1 immunotherapy was investigated in older patients with metastatic melanoma.

Although ICI has been established as a promising treatment strategy for patients with cancer, older cancer patients represent a heterogeneous group as they can vary widely in frailty, cognition and physical status. In **Chapter 5**, the association between clinical frailty and immune-related treatment toxicity (IrTox), hospitalization and treatment discontinuation due to IrTox in older patients treated with checkpoint inhibitors was investigated.

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