Ageing and immunity: unraveling the association between immunosenescence and frailty

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General discussion

GENERAL DISCUSSION

The complex association between immunosenescence and frailty

Collectively, research on immunosenescence, frailty, and age-related diseases highlights the existence of a self-reinforcing cycle that reduces the chances of healthy ageing. Frailty and age-related diseases are closely linked, each increasing the risk of the other. A similar bidirectional relationship exists between immunosenescence and age-related diseases. However, the relationship between frailty and immunosenescence remains unclear. Ageing is marked by biomolecular changes that affect multiple systems, including the immune system, contributing to immunosenescence, which appears to underlie frailty. These overlapping mechanisms suggest that frailty, immunosenescence, and biological ageing are interdependent processes (Figure 1).

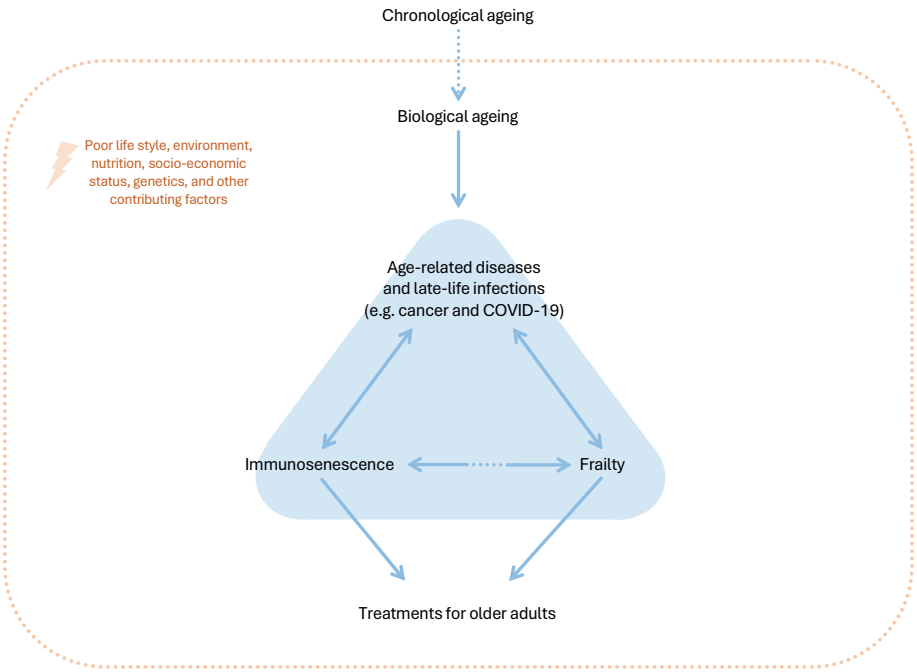

Figure 1. The complex association between immunosenescence and frailty

Several mechanisms potentially linking frailty and immunosenescence have been proposed, but they remain insufficiently studied and lack consistent evidence. In **Chapters 2-4**, we identified several immunological markers related to frailty from prior literature and our research. The most frequently reported markers include

C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α).

Evidence suggests that elevated CRP levels are associated with an increased risk of sarcopenia, cardiovascular diseases, disability, and cognitive decline in older adults. Elevated CRP levels were also associated with increased risk of mortality in frail older patients (1-3). Walker et al. (2017) demonstrated that higher midlife CRP levels predict frailty in later life, emphasizing its role as an early indicator (4). However, the measurement of CRP plasma levels is a frequently used screening test in daily clinical practice. Clinicians use it as a tool to diagnose infections or clinical conditions closely associated with underlying inflammatory mechanisms, in which case CRP levels are much higher (>10 mg/L). Therefore, CRP seems to be a rather nonspecific biomarker of the ageing immune system. IL-6 and TNF-α also play central roles in frailty, particularly in the pathogenesis of chronic and age-related conditions. In acute inflammation, IL-6 facilitates T-cell expansion, B-cell differentiation, and the synthesis of acute-phase reactants such as CRP (5). Studies have linked elevated IL-6 and TNF-α levels with age-related diseases such as dementia and Parkinson's disease, which are commonly seen in frail patients (6, 7).

Immunosenescence involves the remodeling of the T cell compartment, driven by the thymic involution and bone marrow, skewing of immune cells to the myeloid lineage and resulting in substantial changes in the T cell populations. In **Chapter 2**, we also observed that only a limited number of T lymphocyte subpopulations had been studied previously. Among these, lower levels of naïve CD4+ T-cells and effector memory CD8+ T-cells were associated with increased frailty. However, the studies on T lymphocytes were limited in both size and scope. Although initial findings appeared promising, the lack of available data as well as standardized naming and measurement methods for biomarkers complicates comparisons across studies, making it difficult to draw definitive conclusions on their association with frailty. Nevertheless, **in Chapter 4**, when examining melanoma patients receiving anti-PD1 immunotherapy, we observed some of these age- and frailty-associated immune changes, including lower frequencies of CD8+ naïve T cells in older patients and a frailty-associated loss of CD8+ effector tissue-resident-like memory T cells and CD8+ mucosal-associated invariant T cells. These findings highlight that age- and frailty-driven immune remodeling, particularly of T-cell populations, is complex and can extend across diverse clinical settings.

Despite these associations, evidence on useful biomarkers in the clinic to identify frailty remains limited, due to the scarcity of studies and the small patient sample sizes, leading to inconsistent results. Uncovering shared biological pathways between frailty and immunosenescence is particularly challenging, given the complex

interplay with chronic low-grade inflammation, comorbidities and disease-specific factors. For example, elevated levels of inflammatory markers can be triggered by a wide range of conditions, such as diabetes, depression, age-related pain, endocrine disorders and nutritional deficiencies, which can modulate immune responses in diverse ways. The considerable variability in older adults' immune profiles makes it difficult to establish whether these markers are contributors to frailty or are byproducts of underlying disease conditions. The immune profile associated with frailty becomes more complex when influenced by acute or subacute infections, highlighting the importance of investigating the association in the context of specific diseases (Figure 1). Critically, disentangling the causal relationship between immunosenescence and frailty is essential for designing effective interventions, developing appropriate therapeutic strategies and identifying individuals at risk early. Without clarity on causality, there is a risk of misinterpreting association, which could lead to inappropriate clinical decisions.

Immunosenescence in COVID-19

In **Chapter 3**, frail patients paradoxically exhibited lower CRP levels upon hospital admission compared to their non-frail counterparts, even though elevated CRP was associated with increased frailty and mortality risk. These findings challenge conventional understanding. While frailty is a significant factor in determining overall outcomes in older patients, the elevated risk of mortality in older patients with frailty compared to fit patients may not be explained solely by the difference in inflammatory responses.

Indeed, it is also important to take into account that frail patients experience more comorbidities. Some studies suggest that chronic underlying conditions predict mortality risk in COVID-19 infections, which include hypertension, cardiovascular diseases, diabetes, chronic obstructive pulmonary disease, cerebrovascular diseases, renal diseases, obesity, neurodegeneration and highly inflammatory conditions such as cancer and immunosuppression (8-13). Additionally, a systematic review of seven studies showed that patients with COPD, cardiovascular disease and hypertension were at higher risk of severe illness and intensive care unit admission (14). Furthermore, hypertension commonly coexists with Alzheimer's disease, which has also been recognized as a significant comorbidity influencing COVID-19 prognosis (15-17). These conditions predominantly affect older adults, potentially contributing to frailty and heightening their vulnerability to COVID-19 infection (18). As a result, affected patients may present at earlier stages of the disease, hence exhibiting lower CRP levels upon admission.

Although differences in inflammatory responses may not fully explain the increased mortality risk among frail older patients, CRP remains a valuable, rapid, and cost-effective biomarker for its prognostic value in assessing the risk of disease severity. Elevated serum CRP concentrations have been associated with COVID-19 disease progression and poor clinical outcomes (19, 20). However, we should be cautious when interpreting admission CRP levels in frail patients; clinicians must consider clinical history and perform geriatric assessments rather than relying solely on isolated markers. Studies often lack a detailed investigation into the immune and metabolic pathways underlying frailty. COVID-19 involves complex immune and vascular responses, including increased inflammatory markers, cytokine release, coagulation abnormalities, and endothelial dysfunction. Most prior studies have analyzed these biomarkers individually, with few investigating these interconnected pathways collectively, particularly within the context of frailty. Future investigations should include an extensive evaluation of biomarkers related to endothelial dysfunction, coagulation response, systemic inflammation, cytokine and chemokine release, and organ damage. Hence, CRP (trajectories) should be evaluated over time in conjunction with (those of) other biomarkers.

Notably, the dysregulated secretion of cytokines, known as a "cytokine storm," has been recognized as a critical contributor to poor outcomes in COVID-19. This cytokine storm involves an exaggerated inflammatory and immune response, predominantly affecting the pulmonary system and resulting in acute respiratory distress syndrome, pulmonary oedema, and multi-organ failure (21). Alleviating this inflammatory state may improve patients' prognosis. Older patients with comorbidities are particularly susceptible to developing hyperinflammation in the course of the disease, due to their impaired immune function and chronic inflammatory states (22-24).

One signalling pathway that plays a key role in mediating this inflammatory response is the JAK-STAT pathway. In particular, STAT3 activation has been shown to contribute to the development of severe symptoms like cytokine release syndrome in patients with COVID-19. Preclinical evidence suggested that JAK inhibitors may reduce low-grade inflammation in older adults. However, their immunosuppressive effects limit their use in immunocompromised patients or those with cancer (25). JAK inhibitors are also being explored for preventing severe COVID-19 cytokine storms, though results remain inconsistent (26, 27). Several therapeutic agents targeting this pathway, including IL-6 receptor antagonists (e.g., sarilumab), IL-1 receptor antagonists (e.g., anakinra), and JAK inhibitors (e.g., baricitinib, fedratinib, and ruxolitinib), are under investigation (26). So far, vaccination has been the best strategy to stop the viral spread and control the pandemic. However, vaccination might not provide full

protection to the older population due to the age-related decline in immune function (28).

Immunosenescence in melanoma cancer and toxicity of immunotherapy

Several studies suggest that ageing of the immune system compromises the adaptive immune response, particularly T cells, potentially reducing the effectiveness of such treatments. In **Chapter 4**, we found several ageing- and frailty-associated changes among circulating immune cells in blood, but these were not associated with response to immunotherapy in our study. A recent study also showed that aged and younger patients had derived similar clinical outcomes, despite a clear age-related divergence in immune phenotypes (29). It is also possible that the absence of a correlation between immune senescence markers and the treatment response indicates that immune senescence and frailty may not affect the effectiveness of immune checkpoint inhibitors, allowing older adults to respond to immunotherapy comparably to their younger counterparts despite diminished immune function. In fact, initial studies on older patients are quite reassuring. Retrospective studies and meta-analyses have investigated ICI effectiveness in older adults and found no difference in overall survival (OS) or response rate by age (30, 31). Similarly, observational data have shown no differences in treatment response and survival between younger and older patients (32).

However, older patients with geriatric impairments seem to be more likely to experience immune-related adverse event sequelae, and this patient group is usually underrepresented in clinical trials (33, 34). In **Chapter 5**, our findings revealed consistent trends between patients with an abnormal Geriatric-8 test score (of < 15, suggesting significant frailty) or a high WHO score (of ≤ 1, indicating some degree of functional impairment or reduced ability to perform daily activities) for having higher odds of toxicity, treatment discontinuation due to immune-related treatment toxicity, and hospitalization due to immune-related treatment toxicity. Both an abnormal G8 score and a higher WHO performance status were associated with a higher risk of toxicity, hospitalization, and treatment discontinuation due to toxicity. Additionally, severe toxicities were more common in patients with comorbidities, particularly cardiovascular conditions, which showed trends toward higher odds of hospitalization and treatment discontinuation. Similarly, the ELDERS study demonstrated that an abnormal G8 test score < 15 was a predictor of a significantly higher risk of adverse outcomes, such as comorbidity-related hospital admissions and risk of death(35), highlighting that while older patients and those with underlying frailty may experience more severe outcomes during treatment, much of this risk could be tied to their preexisting comorbidities and overall vulnerability, rather than strictly to immune-

related adverse events. In a Dutch national registry study of melanoma patients treated with ICIs, while response rates and grade 3 or higher toxicity rates were not influenced by age or comorbidities, patients aged ≥75 experienced higher rates of treatment discontinuation due to toxicities (36). This suggests that older and frail patients tolerate toxicity less well compared to younger patients and are more likely to discontinue treatment due to side effects, even if they are not necessarily experiencing more toxicities than their younger counterparts. Older patients may lack the physiological reserves needed to fully recover from toxicities, as they tend to be more frail than younger individuals and more likely to have multiple chronic conditions. Additionally, the reduced immune responsiveness in frail patients likely contributes to their decreased capacity to tolerate and recover from mild toxicities. This may suggest a role of frailty as a functional manifestation of immunosenescence.

Although current evidence suggests that older patients respond to immunotherapy at least as well as younger patients, it remains important to develop a more comprehensive panel of biomarkers to better predict treatment response and clinical outcomes. Studies have reported associations between immune-related blood markers, such as elevated neutrophil-to-lymphocyte ratio (NLR) and reduced albumin levels, and worse clinical outcomes across various cancer types (37). However, the findings were limited due to heterogeneous methodologies and small sample sizes. Alterations in immune parameters, including neutrophils, lymphocytes, total white blood cell counts (WBC), and particularly NLR, have been implicated in tumor-promoting and immunosuppressive roles associated with poor outcomes in solid tumors (38-43). Elevated NLR has also been linked to increased frailty in cancer survivors, individuals with cardiovascular disease, and community-dwelling older (44). Dilorom proposed that elevated levels of NLR, total WBC, and neutrophils may reflect an acute inflammatory response driven by cancer pathology and treatment-related stress (38). Additionally, increased circulating myeloid cells, particularly myeloid-derived suppressor cells, have been reported in older and frail patients relative to younger counterparts (45).

Recent laboratory and clinical studies showed that the timing of immunotherapy infusion plays a key role in the treatment outcomes for cancer patients. Multiple studies involving over 6000 patients across several tumor types (melanoma, lung, renal, bladder, liver, etc) consistently report better outcomes when infusions are given in the morning. For example, a melanoma cohort found that morning administration nearly doubled overall survival versus afternoon dosing, and a meta-analysis by Landré et al (2024) reported that early-day administration of immunotherapy doubled progression-free and overall survival compared to later administration. The immune system follows the body's circadian rhythms, with peak activity in the morning. These rhythms modulate immune-cell trafficking, cytokine secretion and T-cell function,

processes targeted by many immunotherapies. In our study, the timing of infusion was not recorded, representing a limitation of the study. Given the accumulating evidence, adequate randomized controlled trials comparing morning, afternoon, and evening administration are warranted to define optimal infusion time and to enable more personalized treatment strategies in oncology.

Challenges and future directions in immunology and frailty research

One of the main challenges in this research is the multifactorial nature of frailty, given the important heterogeneity of the older population and the lack of a uniformly accepted definition.

There remains ongoing debate within the geriatric field regarding the most appropriate instrument for measuring frailty. In associative research and in our studies, the Clinical Frailty Scale (CFS) appeared to be the most suitable tool, not only because it is time- and cost-efficient, but also because its continuous scoring system allows frailty to be quantified along a spectrum rather than dichotomized into frail versus non-frail, enabling stratified analysis that yields insights into underlying mechanistic pathways. This gradation enhances its clinical applicability, enabling a more nuanced assessment of health status. Furthermore, the CFS incorporates both physical and cognitive domains of frailty, in contrast to the Fried phenotype, which focuses exclusively on physical criteria. The clear cut-offs within the CFS (from fit to pre-frail to frail) capture individual variability while remaining practical and resource-efficient for use in clinical and research settings. The CFS has been validated and used across many settings.

Another relevant instrument, which we did not apply but which merits consideration, is the Frailty Index (FI) (46). The FI measures frailty as the accumulation of health deficits, including 30 or more symptoms, signs, disabilities, or diseases (47). Unlike phenotype-based measures, the FI includes a broad range of health-related parameters, many of which are correlated, reflecting the interconnected nature of ageing-related decline. The FI has been shown to behave consistently across diverse study settings, and its continuous nature enables robust prediction of adverse outcomes, including morbidity and mortality (48).

On the other hand, immunological variability is influenced by factors such as genetics, lifestyle, comorbidities and disease exposures, making it difficult to identify consistent immune senescence markers associated with frailty. In addition, standardization in the identification and validation of immune biomarkers is lacking, as differences in assays, methodologies, and marker definitions hinder cross-study comparisons. Future research should prioritize the development of standardized

protocols for immune cell profiling to enhance reproducibility and comparability across studies.

To clarify the relationship between immunosenescence and frailty, longitudinal studies are essential. Following older adults, with repeated measurements of immune markers and frailty levels, would help determine the time course and directionality, as well as the potential causality of immune changes in relation to frailty.

In practice, researchers often begin with cross-sectional analyses to identify candidate biomarkers associated with frailty, and then test these markers in subsequent prospective cohorts to confirm their predictive value. Usually, studies of ageing biomarkers have been hypothesis-driven and single-omic, for example, comparing one or few proteins or cell types between frail and fit individuals. These approaches can be laborious and may miss broader patterns, because ageing is a complex and context-dependent process. The next steps in research would be an in-depth analysis of frailty with multi-omics approaches. Multi-omics strategies use high-throughput, unbiased profiling across many molecular layers (genomics, transcriptomics, proteomics, metabolomics, etc) simultaneously. For example, one large study analyzed thousands of plasma proteins in tens of thousands of UK biobank participants and found that a “youthful” immune-system proteomic profile was uniquely associated with greater longevity (49). Similarly, another group used blood immune markers to train a deep-learning “inflammatory age” clock (iAge) that tracked multimorbidity, immunosenescence and frailty (50). These studies illustrate how combining multiple omics layers can identify novel biomarkers or composite indices of healthy vs unhealthy ageing. Omics-based techniques can offer a more holistic view of biological ageing by integrating inflammatory, immune-metabolic, and cellular ageing markers, preferably at multiple time points.

Such integrative studies of frailty and immunosenescence require rich datasets and careful design. This approach needs a comprehensive clinical and lifestyle data collection, which includes comorbidities, prior treatment, quality of life, nutrition, activity levels, etc. However, the extended follow-up required and the absence of a clear immunological definition for the onset of frailty present methodological challenges. Additionally, studies are often biased due to small sample sizes and non-representative cohorts. Very frail individuals are more likely to drop out due to illness or death, leading to the underrepresentation of frailty, compared to fitter participants, limiting the generalizability. The challenges in this research also lie in the complex interplay of chronic low-grade inflammation, comorbidities, and other age-related conditions that should be taken into account. Moreover, how immune markers are modulated by disease severity remains an important but underexplored question.

In COVID-19, measuring inflammation biomarkers frequently over time may be an optimal strategy to characterize the evolution of the patients' immune response and the progression of the disease. Continuous monitoring of the biomarkers could guide both the timing and dosing of anti-inflammatory interventions, as well as evaluate their efficacy. Older adults with comorbidities or chronic conditions face a higher risk of mortality from COVID-19, underscoring the need for systematic frailty screening and comprehensive clinical history documentation.

Additionally, careful monitoring of comorbidities during hospitalization could help to assess their influence on disease progression and outcomes. This could be addressed by a prospective cohort study that tracks disease severity (e.g. use of mechanical ventilation, admission to intensive care unit) or in-hospital mortality in COVID-19 patients stratified by the type and number of comorbidities and frailty level. Another idea would be assessing the level of protection vaccines provide to frail individuals to enable more accurate predictions of post-vaccination infection rates and morbidity in this vulnerable population. To date, no studies have specifically examined the incidence of infections in frail compared to non-frail individuals.

In melanoma, expanding blood-based multi-biomarker panels are needed to better capture the immune changes. Longitudinal studies in larger cohorts could monitor markers such as NLR, total WBC and myeloid-derived suppressor cells, which have been associated with frailty and poor outcomes in solid tumors, at baseline, during treatment and post-treatment, in relation to frailty, to clarify their clinical significance. Moreover, evaluating the tumor microenvironment should also be considered; however, its characteristics can vary significantly depending on tumor location. Furthermore, special attention must be given to monitoring toxicity in older individuals receiving immunotherapy. Developing immune profiling tools to track immune-related adverse events and tolerance in real time could help optimize safety and efficacy in this population. Considering the heterogeneity in older adults, biomarker strategies could incorporate personalized screening approaches that also account for key clinical parameters such as frailty, comorbidities, polypharmacy, functional status, etc. Assessing frailty over time can also guide decisions regarding treatment intensity or dosage and help identify potential supportive measures for patients (51). Indeed, preemptive dose adjustments, close monitoring, and early initiation of supportive care should be considered, even for toxicities of lower severity. The identification of immune-related adverse events can be particularly challenging due to mental impairment, social issues, or devious symptoms, which could be underreported or assigned to ageing (52). An idea could be to stratify patients, for example, by their (multi-)comorbidities, and monitor them by classification. The comorbidities and frequent polypharmacy make the management of immune-related adverse events challenging. Additionally, immunosuppressive treatments required to manage

immune-related adverse events must be carefully balanced with the patient's existing medication regimen and comorbidities to avoid exacerbating other health issues. Therefore, geriatric assessment could help to identify older patients who are more likely to benefit from immunotherapy with a reduced risk of immune-related adverse events, thereby preventing early treatment discontinuation. Additionally, patient-reported outcomes could be valuable for monitoring and assessing both the toxicities and the impact of immunotherapy on the quality of life in older patients (51).

Potential interventions and broader considerations

Interventions targeting frailty can occur at multiple levels. At a preventive stage, promoting healthy lifestyle behavior, including regular physical activity and balanced nutrition, may delay or mitigate the onset of frailty. Lifestyle factors influence biological ageing and may contribute to building physiological resilience.

At a molecular level, emerging studies are investigating therapeutic strategies that target senescent cells, which are more prevalent in ageing populations and contribute to chronic inflammation through the senescence-associated secretory phenotype (SASP). In preclinical studies, senolytic drugs have shown potential to mitigate SASP-driven inflammation or the “cytokine storm”, also observed in severe COVID-19 cases among older patients (53, 54).

On a societal level, research must become more inclusive. Many existing studies disproportionately represent Caucasian populations, and historically, biomedical research has been predominantly conducted on male subjects (55, 56). Yet emerging studies show that sex- and ethnicity-specific differences exist. For instance, females and individuals from different backgrounds may present different comorbidities burden and social determinants of health that interact with the ageing of the immune system (57-59). Greater inclusion of underrepresented populations is essential to capture the full spectrum of immune ageing and frailty.

Conclusion

A better understanding of the roles of the immune system in ageing and frailty is essential for developing effective therapeutic strategies for age-related diseases, enhancing preparedness for future infectious pandemics, and promoting healthy ageing. Current treatment approaches and decision-making tools remain inadequate for effectively monitoring frail individuals across various disease contexts. Findings from our studies on COVID-19 and melanoma suggest a common need for a personalized approach to treatment in older adults. Integrating geriatric assessment with a broader immune marker panel, rather than relying on isolated markers, may improve the treatment decision process and the prediction of treatment response and adverse events.

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