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Ageing and immunity: unraveling the association between immunosenescence and frailty

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English summary

Nederlandse samenvatting

List of publications

Curriculum Vitae

Acknowledgements

ENGLISH SUMMARY

The overall aim of this thesis was to uncover how age-related changes in the immune system are associated with frailty and risk for adverse outcomes of two prevalent age-related disease paradigms: cancer (more specifically, melanoma) and COVID-19.

As age-related changes in the innate and adaptive immune system are thought to contribute to frailty, in **Chapter 2**, we explored the potential immunological determinants correlated to frailty in the literature. The most frequently studied inflammaging biomarkers were IL-6, CRP and TNF- α . Different types of T-lymphocyte subpopulations were studied, but each subset was studied only once. The findings revealed IL-6 and CRP to be consistently associated with frailty. Some studies showed an association between different T-lymphocyte subpopulations and frailty, including lower levels of naïve CD4+ T-cells and effector memory CD8+ T-cells with higher frailty; however, the number of investigations per cell subpopulation was too few, preventing us from drawing strong conclusions.

In **Chapter 3**, we examined the association of frailty with inflammatory markers and the role of frailty in the relationship between these markers and in-hospital mortality among older patients hospitalized for COVID-19. In all cohorts studied, lower CRP levels were associated with higher frailty scores, whereas higher CRP levels were associated with increased in-hospital mortality risk across frailty groups. The association of low CRP with higher frailty may be explained by patients with high frailty tending to present themselves at earlier stages of disease. In the interaction term analysis, frailty did not modify the association between inflammatory markers and in-hospital mortality. While frailty was a significant factor in determining overall outcomes in older patients, the findings suggest that the elevated risk of mortality in older patients with frailty compared to fit patients is likely not explained by differences in inflammatory responses.

In **Chapter 4**, we shifted our focus to melanoma, particularly in the context of immune checkpoint inhibitors (ICIs), which are increasingly used in older cancer patients. Several studies suggest that ageing of the immune system compromises the adaptive immune response, particularly T cells, potentially reducing the effectiveness of ICI treatment. To explore this hypothesis, we investigated the association between immune senescence markers in blood cells and age, frailty, and response to anti-PD-1 therapy in older patients with metastatic melanoma. Older patients, irrespective of frailty, showed lower levels of naïve CD8+ T cells, with the old and frail group also exhibiting reduced tissue-resident effector memory CD8+ T cells and CD8+ mucosal-associated invariant T (MAIT) cells. These differences were not associated with treatment outcomes. T cell proliferation and antigen-presenting cell capacities

did not differ across groups. These findings suggest that the level of frailty and ageing may not necessarily compromise the efficacy of ICI therapy.

Chapter 5 addressed the broader challenges faced by older patients with cancer undergoing ICI treatment. We investigated the association between frailty and immune-related treatment toxicity, hospitalization and treatment discontinuation due to immune-related treatment toxicity in older patients treated with checkpoint inhibitors. The 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 risk of toxicity, treatment discontinuation due to immune-related treatment toxicity, and hospitalization due to immune-related treatment toxicity, although not statistically significant. Moreover, in a sub-analysis, we observed that the treatment discontinuation due to immune-related treatment toxicity occurred often in frail patients with grade 1-2 toxicity, suggesting a lower tolerance of toxicity in frail older patients.