Proteomic aging biomarkers predict survival in immunotherapy-treated tumors

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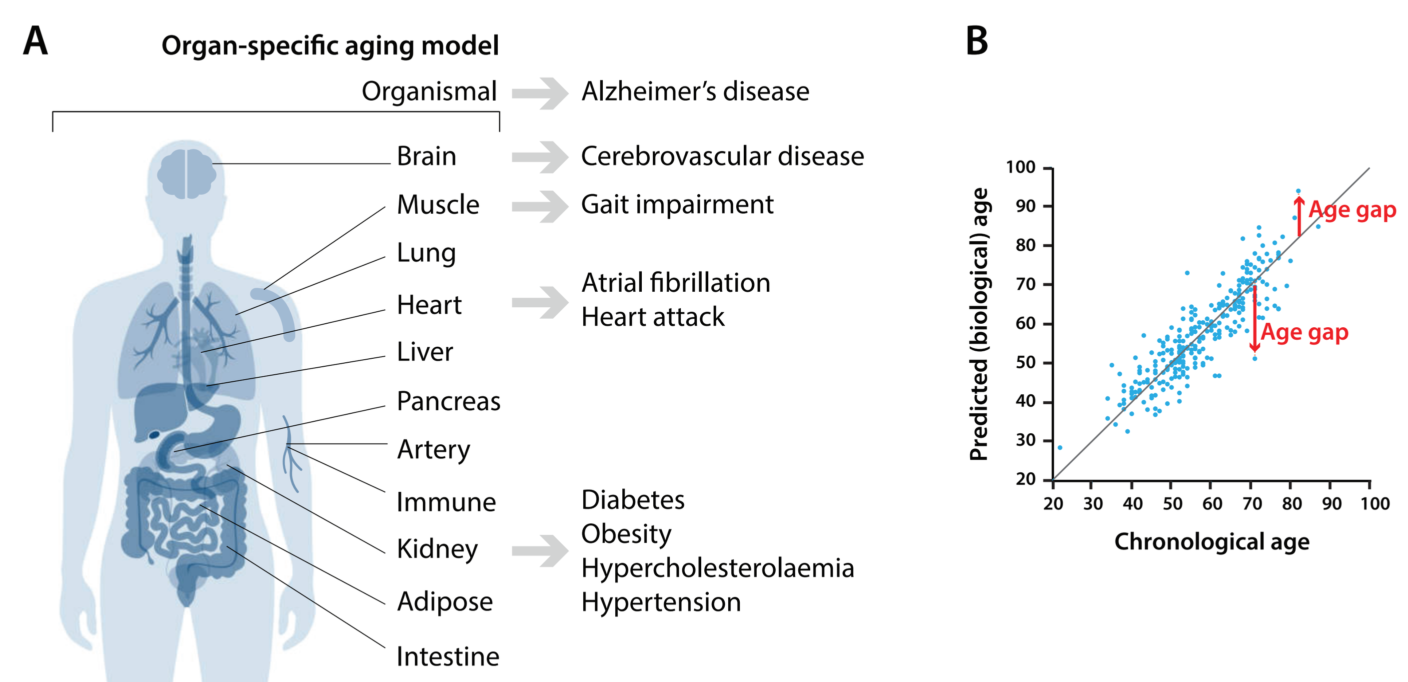
Background

Plasma proteomics provides a comprehensive view of active biological processes in an individual. Studies in healthy populations have shown that the plasma proteome undergoes changes with aging, and that proteomics-based models can predict biological age. Here, we examined age-associated effects on the plasma proteome of cancer patients across multiple tumor types. Applying previously described plasma proteomics-based aging models, we identify links between aging, tumor characteristics, and clinical features.

Plasma proteomics-based models predict age and disease



A. A previous study by Oh et al. (2023) utilized organ-specific plasma proteins to develop models that estimate aging at the organismal level and in 11 major organs. The study demonstrates that accelerated aging of individual organs is associated with organ-related disorders [1].
B. The difference between the predicted (biological) age and chronological age is known as the "age gap". Several studies have shown associations between age gaps and age-related risks such as disease, mortality and poor clinical prognosis [1-3].

References
[1] Oh et al. Organ aging signatures in the plasma proteome track health and disease. Nature 624 (2023)
[2] Lehallier et al. Undulating changes in human plasma proteome profiles across the lifespan. Nat. Med. 25 (2019)
[3] Rutledge et al. Measuring biological age using omics data. Nat. Rev. Genet. 23 (2022)

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Methods

- Baseline plasma samples were collected from immune checkpoint inhibitor-treated patients with metastatic solid tumors (non–small cell lung cancer [NSCLC], n=818; small cell lung cancer [SCLC], n=99; renal cell carcinoma [RCC], n=297; melanoma, n=163) and healthy subjects (n=278).
- Deep plasma proteomic profiling was performed using an aptamer-based assay.
- Bioinformatic analyses were used to identify age-associated proteomic signatures.
- Organismal and organ-specific predictors were applied to estimate biological age for each patient and organ.

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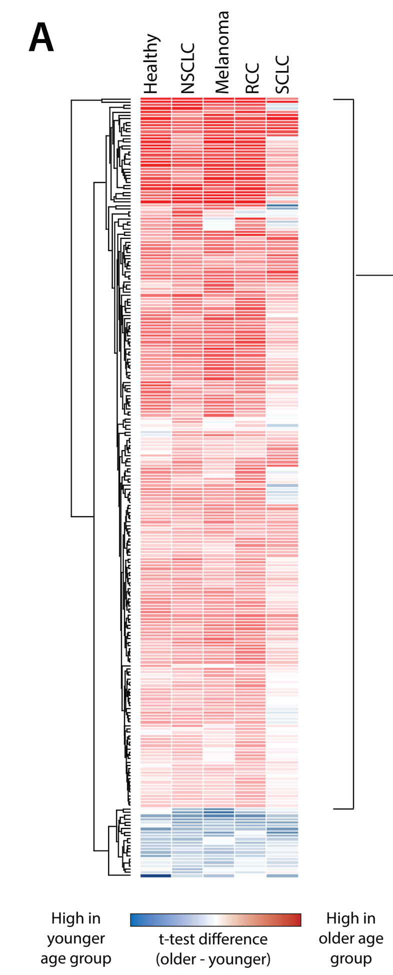
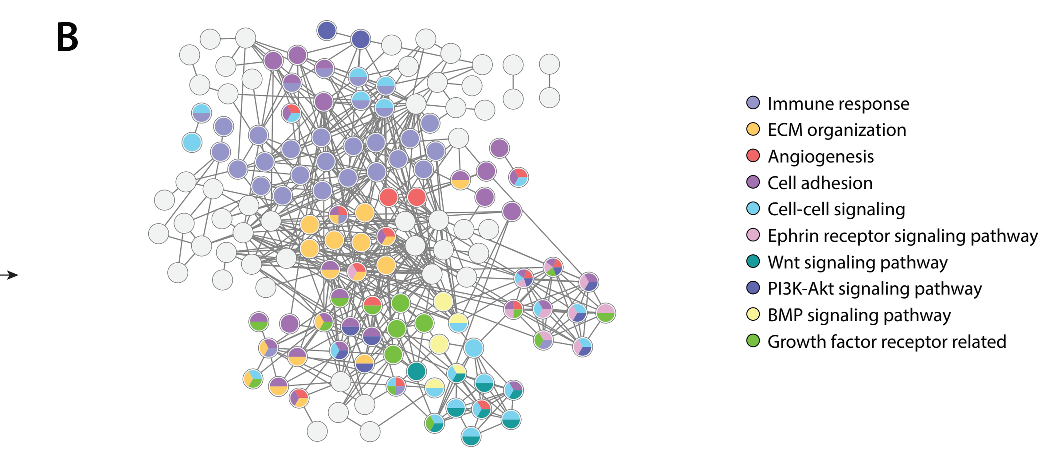
Age-based proteomic profiles are consistent across healthy and cancer populations





Healthy individuals and patients with metastatic cancers were classified into older (≥65 years) or younger (<65 years) age groups. Plasma proteins exhibiting differential expression between the two groups were analyzed.
A. Hierarchical clustering of the t-test difference between mean expression in older and younger age groups (FDR <0.01). The heatmap shows similar trends in proteomic profiles across all cohorts.
B. Proteins upregulated in older individuals are involved in immune remodeling, ECM breakdown, and oncogenic signaling pathway dysregulation, all of which have been linked to aging.

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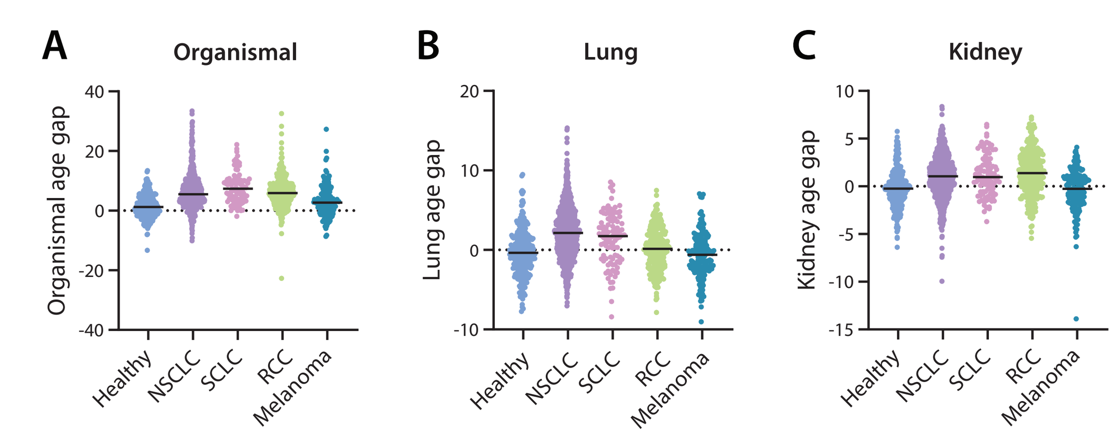
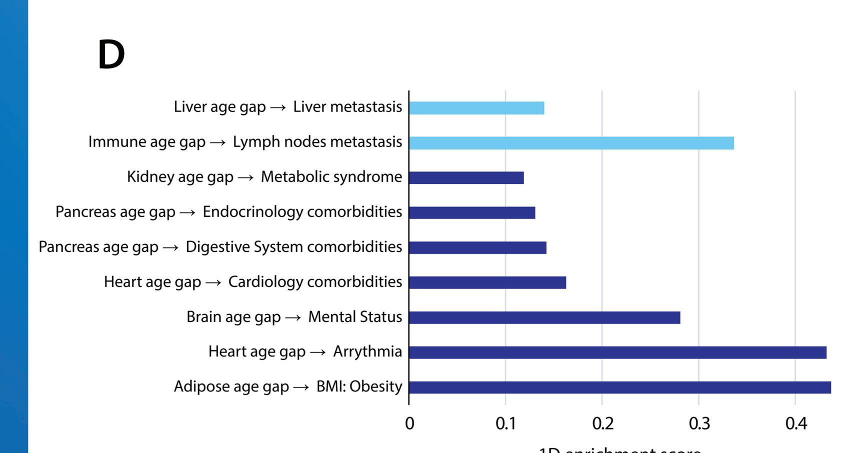
Organ-specific aging is associated with cancer type and comorbidities

Previously described organismal and organ-specific predictors [1] were applied to the current cohorts to estimate biological ages per individual and organ.





A. The organismal biological age gap was significantly higher in all cancer cohorts versus healthy controls, largest in SCLC and smallest in melanoma.
B-C. Organ-level analyses revealed distinct patterns: lung age gap was highest in NSCLC and SCLC, and kidney age gap was most significant in RCC.
D. An enrichment analysis revealed several associations between organ-specific age gaps and corresponding comorbidities but few with organ-specific metastases.

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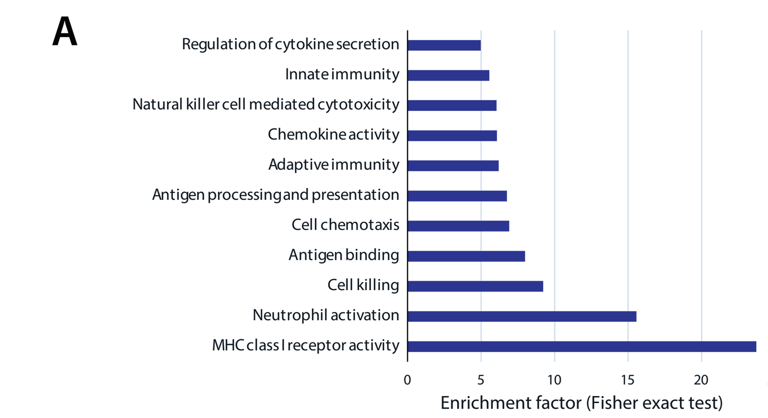
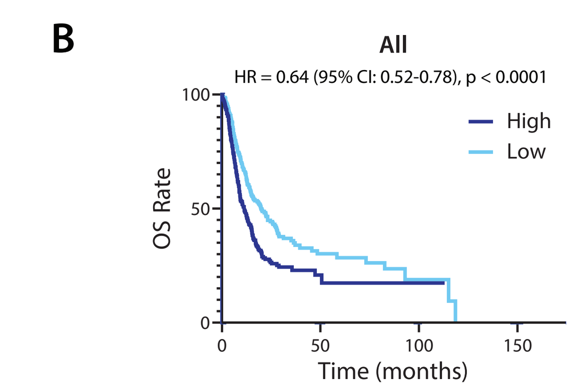
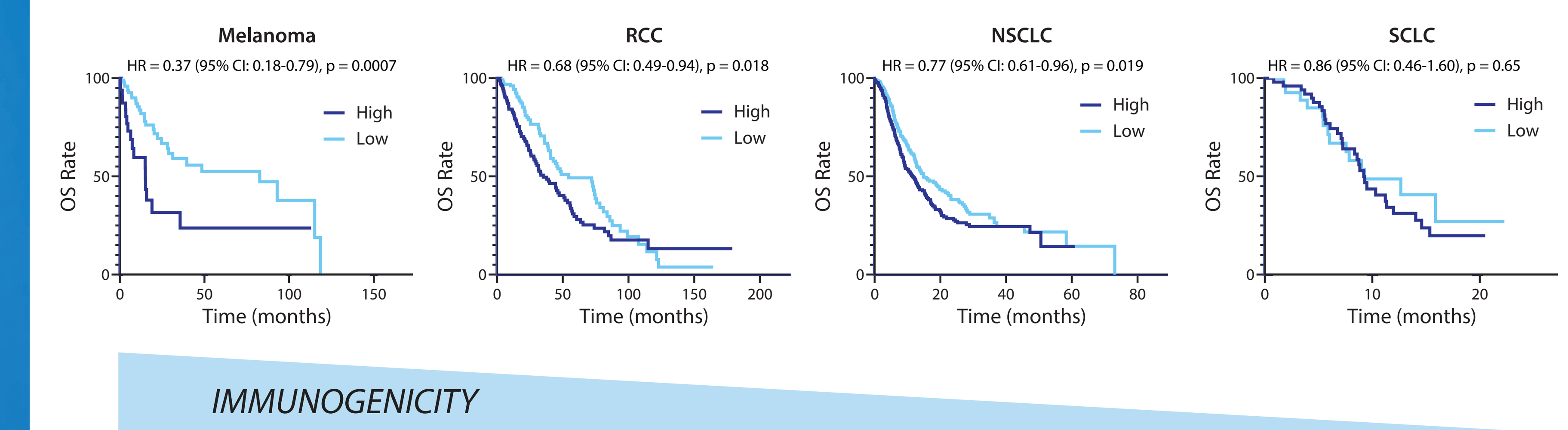
Immune age is associated with survival of cancer patients treated with immune checkpoint inhibitors



A. The immune age predictor [1] is based on a signature of 169 plasma proteins. The signature is significantly enriched with immune-related proteins.
(Fisher exact test FDR < 0.1)



	Median OS (months)	
	High	Low
All cohorts	11.3	19.9
Melanoma	15.1	82.6
RCC	35.3	54.4
NSCLC	11.5	15.0
SCLC	9.2	9.3



B. The immune age predictor was applied to the four cancer cohorts treated with immune checkpoint inhibitors. The median immune age gap was used to stratify patients into two groups. Patients with an immune age gap above the median were classified as "high" and those with an immune age gap below the median were classified as "low". Overall survival (OS) was assessed.
- Overall, patients who exhibited a high immune age gap had significantly shorter OS compared with patients with a low immune age gap.
- The effect varied per cancer type, being strongest in melanoma (known to be highly immunogenic) and absent in SCLC (considered to have low immunogenicity).

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Conclusions

Plasma proteomic aging predictors capture systemic and organ-specific aging processes in cancer. Distinct age-gap patterns across tumor types, along with their association with survival and comorbidities, highlight the biological and clinical relevance of proteomic aging models in oncology.

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