The SASP as Frailty Biomarkers in Newly Diagnosed Multiple Myeloma

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INTRODUCTION

- Frailty is predictive of adverse outcomes in patients with newly diagnosed multiple myeloma (NDMM), but a widely accepted frailty biomarker in MM is lacking.
- Cellular senescence is a mediator of frailty, characterized by secretion of a senescence-associated secretory phenotype (SASP).
- Several SASP molecules correlate with frailty and predict outcomes in patients
- with chronic diseases (Schafer et al. 2020).

OBJECTIVE

- We conducted this study to evaluate the role of SASP in predicting frailty and overall survival (OS) in patients with NDMM.

METHODS

- We used stored plasma samples for 59 patients with NDMM between 2010-2017 and measured the concentration of 39 SASP factors by Luminex multiplexed bead-based assays and ELISA.
- We studied the association between SASP molecules and a cumulative deficit frailty index (FI) using partial spearman's correlation coefficients, and OS using multivariate cox proportional hazards.
- P-values <0.05 were considered statistically significant.
- We assessed the predictive ability of each measure on OS using time-dependent ROC curve analysis.

RESULTS

- The median age was 60 years. 39% were frail.
- Patients received PI-based (27%), IMiD-based (37%), and PI+IMiD-based induction (36%).
- SASP molecules: TNF-RI, TNF-RII, IL-6, IL-8, MMP-9, uPAR, osteoactivin, GDF-15, Fas, MPO, and Activin A had a significant positive correlation with the FI after adjusting for age, ISS stage, and High-Risk FISH **(Figure 1)**.
- Median follow-up was 5.0 years.
- TNF-RI, TNF-RII, IL-8, GDF-1, VEGF, ICAM-1, RAGE, uPAR, osteopontin, Activin A, and Fas were all predictive of decreased OS after adjusting for age and FI.
- A panel of 5 SASP factors had higher predictive ability for OS than TNFR1 alone, age, and the frailty index **(Figure 2**).

RESULTS

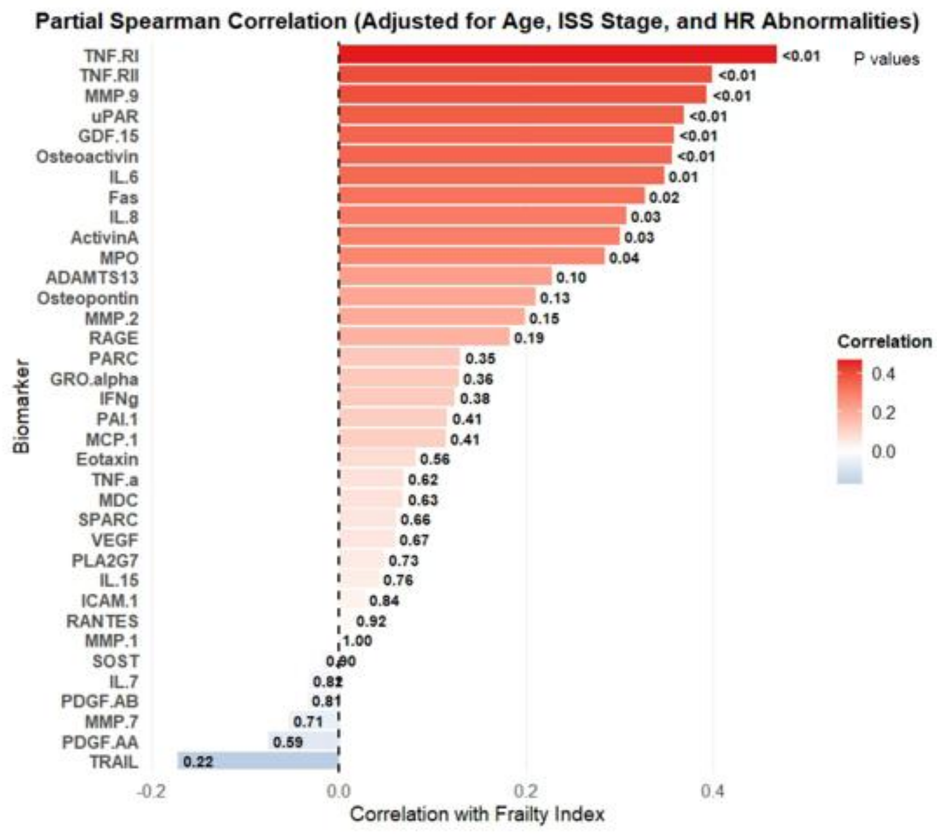

Figure 1: Correlation between SASP protein levels and a cumulative deficit frailty index, adjusted for age, ISS stage (III vs I/II), and High-Risk FISH. High-risk FISH was defined by the presence of ≥1 of the following: high-risk immunoglobulin (IgG) translocation (t[4;14], t[14;16], or t[14;20] translocation), deletion 17p, and 1q gain/amplification. We included 32 deficits for the calculation of the frailty index as previously described (*Abdallah et al. 2025*), including patient-reported ADLs/IADLs, comorbidities and BMI. A higher frailty index indicates a more frail state.

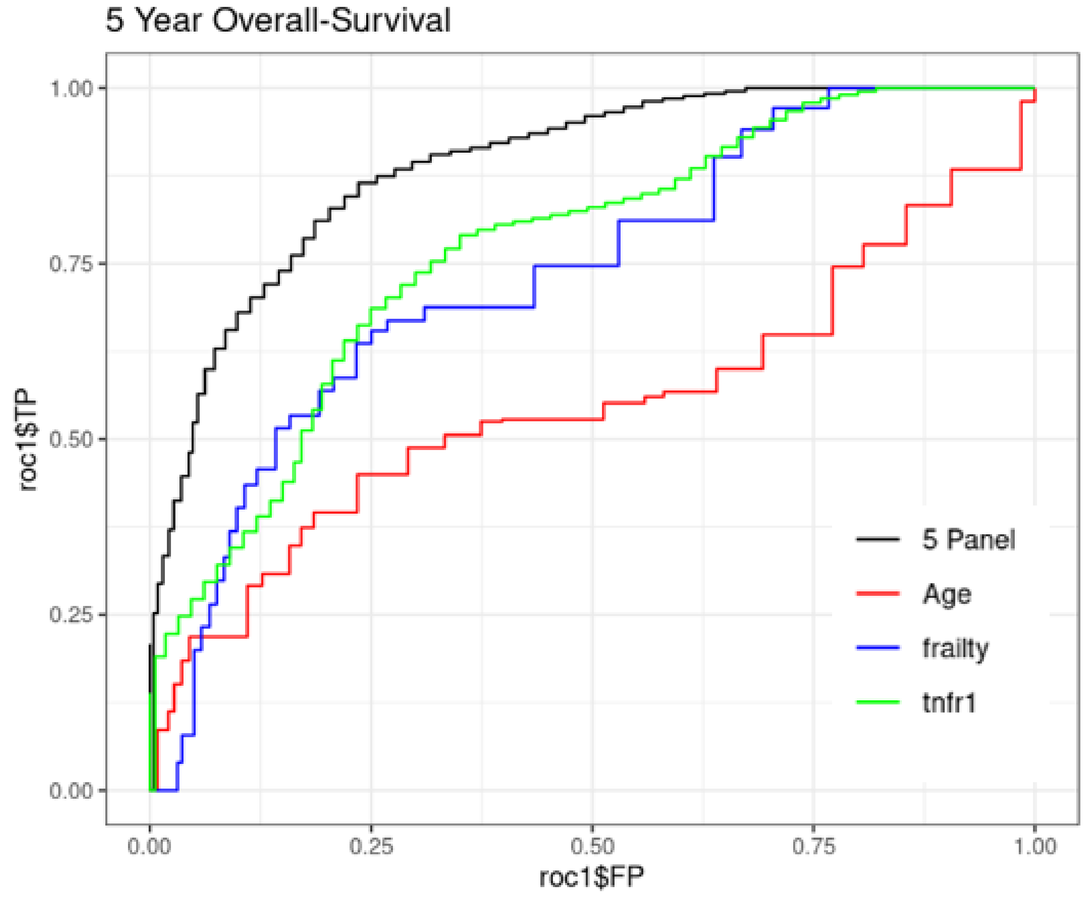

Figure 2: Receiver operating characteristic (ROC) curves for predicting 5-year overall survival in patients with NDMM.

CONCLUSION

- Several SASP molecules are positively correlated with frailty and independently associated with decreased OS, suggesting a role for inflammaging in mediating frailty in MM.
- These results warrant further investigation of SASP molecules as objective biomarkers to guide treatment in NDMM.

REFERENCES

Schafer MJ, et al. The senescence-associated secretome as an indicator of age and medical risk. JCI Insight. 2020 Jun 18;5(12):e133668. doi: 10.1172/jci.insight.133668. PMID: 32554926; PMCID: PMC7406245.