Multidimensional-Based Approaches to Identify Biological, Clinical and Cognitive Determinants of Frailty: Insights from the Novara Cohort Study

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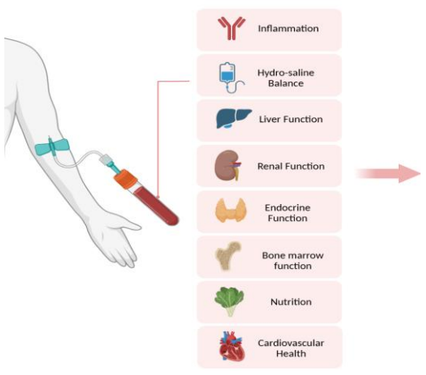
BACKGROUND

Aging poses a significant global challenge, with individuals over 60 expected to constitute 22% of the population by 2050. This shift leads to increased frailty and age-related conditions, burdening healthcare systems. Frailty, a state of vulnerability associated with aging, is linked to adverse outcomes like disability, hospitalization, and mortality, highlighting the need for precise assessments. Traditional frailty measures like the Clinical Frailty Scale (CFS) and the Short Physical Performance Battery (SPPB) offer useful insights but lack the comprehensiveness needed to capture the complexity of aging. Newer tools, such as the Frailty Index (FI) and the Frailty Index Laboratory (FI-Lab), enhance the precision of frailty assessments by incorporating clinical and lab data, with FI-Lab emerging as a simple, reliable predictor of mortality using routine blood tests. Beyond physical frailty, cognitive frailty - combining physical frailty with cognitive impairment - presents additional risks. Tools like the Montreal Cognitive Assessment (MoCA) and the Cognitive Reserve Index Questionnaire (CRIq) assess cognitive function and reserve, providing a broader understanding of an individual's cognitive resilience and aging trajectory. Integrating assessments of both physical and cognitive frailty offers a more comprehensive approach to predict health outcomes and guide interventions. In Italy, the AGING Project, led by the University of Eastern Piedmont, aims to investigate the determinants of healthy aging through the Novara Cohort Study (NCS), Northern Italy's first longitudinal aging study. This multidisciplinary effort seeks to develop strategies to enhance well-being and longevity.

AIM of the STUDY

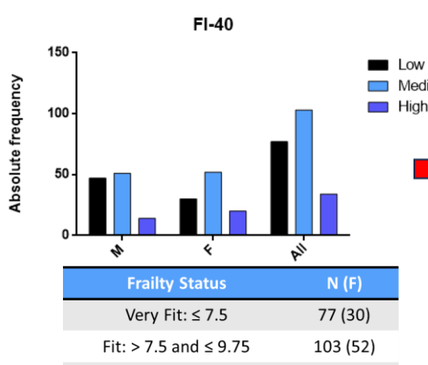
This study aims to develop and validate a comprehensive set of biomarkers and assessment tools to improve the prediction and early detection of frailty and accelerated aging. By integrating clinical evaluations, blood tests, physical and cognitive assessments, the research seeks to create a multi-dimensional approach for assessing frailty and predicting health outcomes. The final goal is to identify blood markers underlying subclinical deficits, enhancing traditional frailty assessments and enabling early interventions to maintain optimal physiological function, reduce healthcare costs, and improve patient outcomes.

Comprehensive frailty assessment in the NCS cohort



A comprehensive literature review was conducted to identify relevant biochemical markers associated with frailty and accelerated aging. The selection of 76 specific markers was determined through a thorough analysis of previous studies considering the frequency of marker uses in frailty research, the informative value of each marker in assessing frailty status, and the availability of standardized procedures for their measurement.
***#** absolute value (abs); **[]** concentration (conc); **%** percentage (per)

Alanine Aminotransferase (ala)	Fibrinogen (fbg)
Aspartate Aminotransferase (alt)	D-dimer (dd)
Gamma Glutamyl Transferase (ggt)	White Blood Cells (wbc)
Alkaline Phosphatase (alp)	Red Blood Cells (rbc)
Bilirubin (bil)	Hemoglobin (hgb)
Blood Urea Nitrogen (bun)	Hematocrit (hct)
Creatinine (cr)	Platelets (plt)
C-Reactive Protein (crp)	Neutrophils %; # (neu)
Uric Acid (ua)	Lymphocytes %; # (lym)
Ferritin (fer)	Monocytes %; # (mono)
Folic Acid (fa)	Eosinophils %; # (eos)
Calcium (ca)	Basophils %; # (baso)
Phosphorus (p)	Erythroblasts %; # (eb)
Potassium(k)	RCDW-CV
Sodium (na)	RCDW-SD
Vitamin B12 (b12)	Mean Platelet Volume (mpv)
Total Cholesterol (tc)	Platelet Larger Cell Ratio (plcr)
High Density Lipoproteins (hdl)	Mean Corpuscular Volume (mcv)
Low Density Lipoproteins (ldl)	Mean Corpuscular Hemoglobin (mch)
Triglycerides (tg)	MCH Concentration
Tyroid stimulating hormone (tsh)	Platelet Distribution Width (pdw)
Transferrin (trf)	Immature Granulocytes (ig)
Albumin % ; [] (alb)	Glycated Hemoglobin %; [ ] (hb1ac)
Cystatin C (cysc)	Homocysteine (hcy)
Alpha1 (a1)	Gamma (g)
Alpha2 (a2)	A/G ratio (ag)
Beta1 (b1)	Total Proteins (tp)
Beta2 (b2)	Haptoglobin
Troponin T (tt)	Iron (fe)
Apolipoprotein A1 (apoa)	Apolipoprotein B (apob)
APOB/APOA1	Cortisol
PT-INR, PT sec, PT ratio	APTT sec, APTT ratio



- ✓ ADL, activity of daily living
- ✓ IADL, instrumental activity of daily living
- ✓ MNA, Mini Nutritional Assessment
- ✓ Health perception
- ✓ Mobility
- ✓ Psychological aspects
- ✓ Physical tests
- ✓ Chronic conditions and diseases
- ✓ Anthropometric parameters

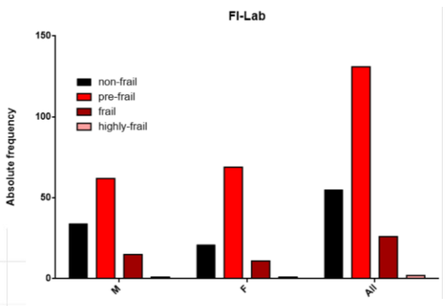
OBJECTIVE COMPREHENSIVE WELL-DEFINED

Frailty Status	N (F)
Very Fit: ≤ 7.5	77 (30)
Fit: > 7.5 and ≤ 9.75	103 (52)
Pre-frail: > 9.75	34 (20)

Distribution of frailty statuses based on FI-40 within NCS group. Each cluster column represents a specific frailty category, with the height of the column indicating the number of individuals within that category.

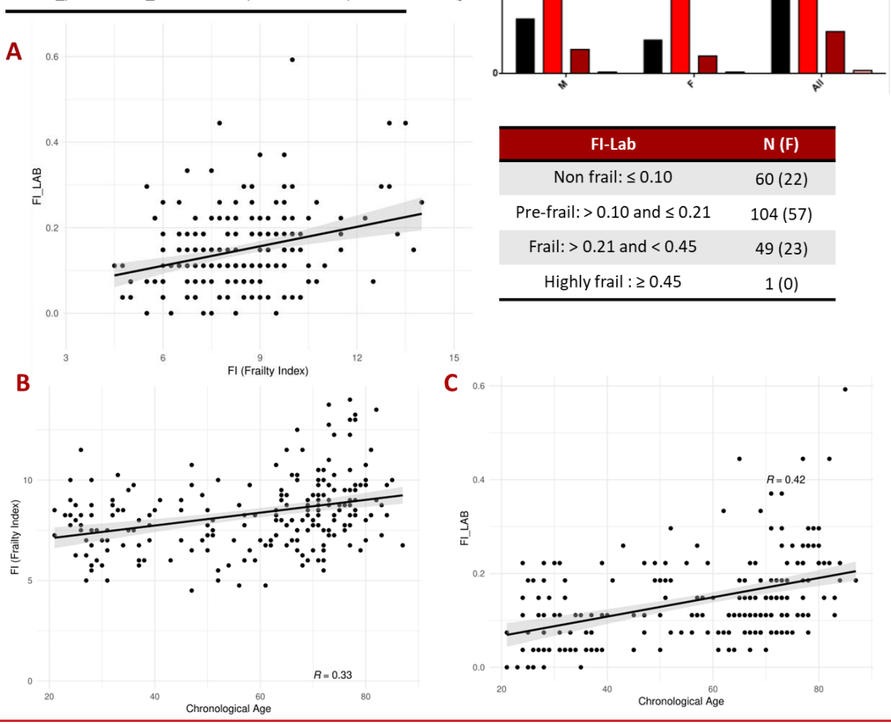
FI-LAB Construction: Exploring Correlations with FI and Age

Selected Variables			
wbc	cr	pt_ratio	alb_per
mchc	bun	a1	a2
rdwcv	egfr	b1	tt
neu_per	cysc	alp	fer
neu_abs	tg	hp	fbg
lym_per	tc	crp	dd
baso_per	alb_conc	apoa	apob



FI-Lab	N (F)
Non frail: ≤ 0.10	60 (22)
Pre-frail: > 0.10 and ≤ 0.21	104 (57)
Frail: > 0.21 and < 0.45	49 (23)
Highly frail : ≥ 0.45	1 (0)

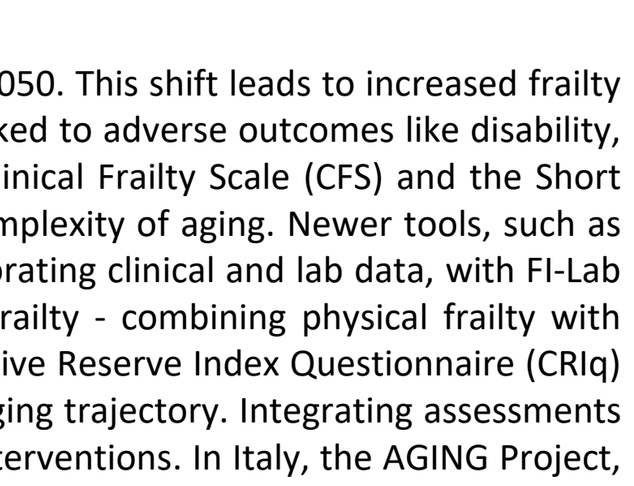
Distribution of frailty statuses based on FI-LAB within NCS cohort. Each cluster column represents a specific frailty category, with the height of the column indicating the number of individuals within that category.



(A) Distribution of FI-LAB values as a function of FI. Pearson coefficient of 0.3 ($p < 0.001$).
(B) Distribution of FI values as a function of chronological age. Pearson coefficient of 0.33 ($p < 0.001$).
(C) Distribution of FI-LAB as a function of chronological age. Pearson coefficient of 0.42 ($p < 0.001$).

Development of a Blood Marker Signature and Predictive Model for Clinical Frailty

	Univariate		Multivariate		
Variable	Coefficients	P value	Variable	Coefficients	P value
wbc	0.33	p < 0.001	cr	-5.09	p < 0.001
mchc	-0.35	0.017	egfr	-0.04	0.012
rdwsd	0.12	0.006			
rdwcv	0.37	0.002			
neu_per	0.04	0.004			
lym_per	-0.04	0.007			
baso_per	-0.80	0.020			
neu_abs	0.46	p < 0.001			
pt_ratio	1.80	0.019			
fbg	0.01	p < 0.001			
dd	0.00	0.003			
bun	0.08	0.004			
egfr	-0.02	p < 0.001			
alb_conc	-1.38	0.005			
tg	0.01	0.001			
alp	0.02	0.037			
crp	1.07	0.004			
tt	0.07	0.001			
hp	0.01	0.001			
cysc	2.05	p < 0.001			
alb_per	-0.13	0.001			
a1	0.97	p < 0.001			
a2	0.35	p < 0.001			
b1	0.35	0.014			
ag	-1.91	0.002			



Volcano plots illustrate the significant variables identified from univariate and multivariate linear regression analyses of the 76 variables with the FI scores. Plot **(1)** represents the results of the univariate analysis, highlighting variables individually associated with FI, while plot **(2)** shows the results from the multivariate model, which accounts for the combined effects of the variables. These visualizations help to identify key predictors of frailty.

(A)

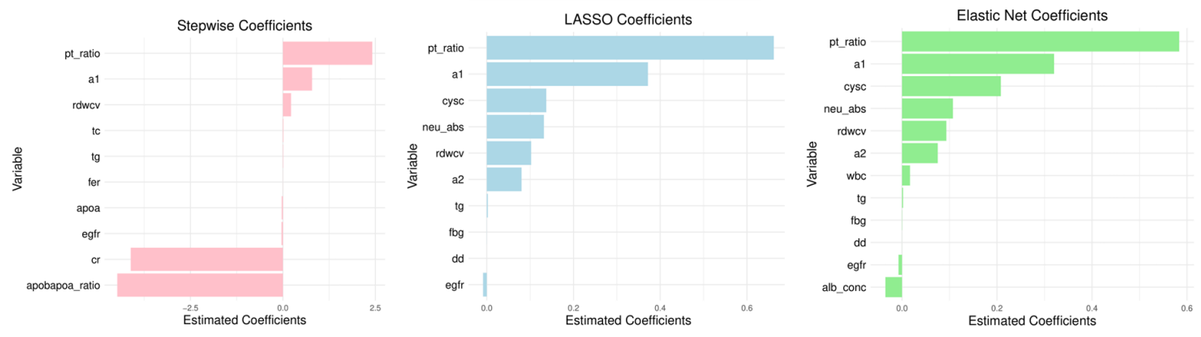
Variable	Stepwise	
	Coefficients	P value
neu_abs	0.20	0.039
egfr	-0.04	p < 0.001
cr	-4.41	p < 0.001
a1	0.75	p < 0.001
tg	0.01	p < 0.001
pt_ratio	2.23	0.001
apoa	-0.02	0.002
rdwcv	0.22	0.045
tc	0.02	0.011
fer	0.002	0.029
apob	-0.04	0.002

(B)

Variable	LASSO
	Coefficients
rdwcv	0.10
neu_abs	0.13
pt_ratio	0.66
fbg	0.0002
egfr	-0.01
tg	0.002
cysc	0.14
a1	0.37
a2	0.08

(C)

Variable	Elastic Net
	Coefficients
wbc	0.02
rdwcv	0.09
neu_abs	0.11
pt_ratio	0.58
fbg	0.0004
dd	1.67
egfr	-0.01
alb_conc	-0.03
tg	0.002
cysc	0.21
a1	0.32
a2	0.075



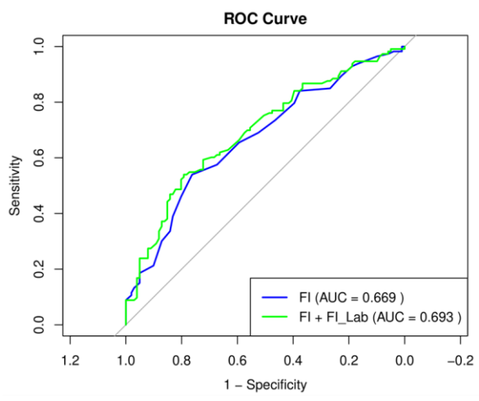
The graphs display the significant variables selected from stepwise **(A)**, LASSO **(B)**, and Elastic Net **(C)** analyses, based on the relationship between 76 variables and Frailty Index (FI) scores. These models highlight the most relevant predictors of frailty by employing different selection methods, offering insights into which variables contribute most to FI in each approach.

Enhancing Cognitive Decline Prediction with Combined FI-40 and FI-Lab Models

MoCA COGNITION

MoCA is validated as a highly sensitive tool for early detection of mild cognitive impairment (MCI)

MoCA Full assesses:
- Short-term memory
- Visuospatial abilities
- Executive functions
- Attention, concentration, and working memory
- Language
- Orientation to time and place



Integrated Discrimination Improvement (IDI) = 2.4%
Net Reclassification Improvement (NRI) = 6%

The image represents the ROC curve of the logistic regression model using the FI alone to predict cognitive decline, as measured by the MOCA test (cut-off for normality ≥ 26), compared to the combined FI + FI-Lab model. The curves indicate a slight improvement in the prediction of cognitive impairment when using the combined model. Key metrics include the area under the curve (AUC = 0.693), integrated discrimination improvement (IDI = 2.4%), and net reclassification improvement (NRI = 6%), demonstrating enhanced predictive accuracy with the addition of FI-Lab.

CONCLUSION

The integration of frailty scales like FI-40 and FI-Lab provides a more comprehensive assessment of frailty, improving the prediction of negative health outcomes. Our findings underscore the importance of biological, lifestyle, and environmental factors in aging, offering valuable insights for both scientific research and public health strategies. This multi-faceted approach will potentially facilitate early identification of individuals at higher risk for poor health outcomes and could pave the way for targeted interventions. Future research will focus on expanding these findings to broader populations, further evaluating the predictive power of the indexes for cognitive decline, and exploring biological mechanisms through proteomic, metabolomic, and immunological analyses.

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