A Frailty Index Based on Routinely Collected Laboratory Safety Data Predicts Dropout in Alzheimer Disease Clinical Trial Settings

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Background

Frailty can be quantified as a frailty index (FI) based on the accumulation of clinically apparent health deficits. Our group has shown that an FI can also be constructed with deficits from **routine blood work and vital signs (FI-Lab)** [1]. Here, we constructed an FI-Lab using lab safety data from the Coalition Against Major Diseases database (CAMD) [2].

Our objective was to explore the relationship between frailty and dropout in Alzheimer disease (AD) clinical trials.

Methods

Design and subjects
- The CAMD database consists of control arm data from 24 trials for Alzheimer disease, with 6500 subjects. Of these, 23 studies (6278 subjects) reported lab test data.
- One study did not report subject dropout timing data, so was excluded, leaving 6160 subjects (**Table 1**).

Frailty Index construction
- With the FI-Lab, we excluded uncommon tests (over 100 tests which were measured in <2000 subjects) yielding 55 unique lab tests (**Table 2**).
- The FI-Lab was constructed for each subject using all available lab tests at screening (20-50 items/subject; median 40).
- Each item was scored as 0 or 1 for normal or abnormal measurements. Normal lab test ranges were included for most studies; missing normal ranges were imputed.

Statistical analysis
- Kaplan-Meier survival curves were constructed to test the univariable association between dropout and high/low frailty (stratified by median FI-Lab score).
- Cox regression was used to model dropout as a function of FI-Lab, age, sex, baseline MMSE score, and the usage of background dementia medication (cholinesterase inhibitors and/or memantine). Study ID was included as a random effect.

Table 1. Demographics and subject characteristics for the 22 trials.

Study ID	Duration, weeks	# subjects	% female	Age*, median (range)	Baseline MMSE, mean (SD)	% background medication	FI-Lab, mean (SD)	% dropout
1009	12	164	55.5%	75 (60-86)	20.6 (3.8)	0%	0.07 (0.06)	11.6%
1013	78	714	50.1%	76 (51-90+)	20.6 (3.3)	82%	0.14 (0.08)	25.2%
1014	78	641	56.5%	76 (50-90+)	21.2 (3.4)	78%	0.14 (0.08)	40.6%
1055	52	134	56.7%	74 (45-87)	19.5 (3.9)	0%	0.10 (0.06)	23.1%
1056	54	487	56.1%	73 (52-90+)	19.8 (4.2)	100%	0.06 (0.05)	25.9%
1057	54	499	61.3%	76 (50-90+)	19.4 (4.0)	100%	0.06 (0.05)	27.5%
1058	24	166	59.0%	73 (50-88)	19.5 (4.2)	0%	0.06 (0.05)	21.1%
1105	78	279	50.2%	74 (50-90+)	20.8 (3.6)	100%	0.10 (0.05)	24.4%
1107	24	144	61.1%	75 (48-89)	12.2 (3.8)	0%	0.07 (0.04)	13.2%
1131	24	56	58.9%	77 (52-90+)	24.4 (1.3)	0%	0.11 (0.04)	17.9%
1132	52	408	43.9%	72 (45-90+)	26.9 (1.7)	0%	0.10 (0.05)	33.1%
1133	30	160	61.2%	74 (56-88)	19.2 (4.7)	0%	0.06 (0.03)	20.0%
1134	24	105	81.9%	88 (65-90+)	14.3 (5.7)	0%	0.08 (0.05)	25.7%
1135	30	268	55.2%	71 (50-89)	19.8 (4.3)	0%	0.07 (0.04)	19.4%
1136	52	143	59.4%	74 (51-88)	19.3 (4.6)	0%	0.12 (0.08)	32.2%
1137	24	215	50.7%	77 (54-90+)	17.0 (3.6)	100%	0.12 (0.06)	11.6%
1138	24	200	57.0%	78 (51-90+)	17.2 (3.4)	0%	0.15 (0.06)	16.5%
1139	24	167	67.7%	80 (50-90+)	7.4 (3.6)	0%	0.15 (0.07)	24.0%
1141	104	486	55.6%	70 (50-90+)	-	0%	0.09 (0.05)	35.4%
1142	78	407	56.3%	78 (54-90+)	20.9 (3.5)	94%	0.07 (0.04)	17.0%
1143	24	103	83.5%	81 (59-90+)	8.0 (3.3)	0%	0.18 (0.09)	20.4%
1144	54	214	64.5%	76 (50-90+)	17.1 (2.9)	0%	0.06 (0.05)	25.7%
All	**-**	**6160**	**56.5%**	**75 (45-90+)**	**19.5 (5.2)**	**48%**	**0.10 (0.07)**	**25.8%**

* Ages above 89 are anonymized in the CAMD database.

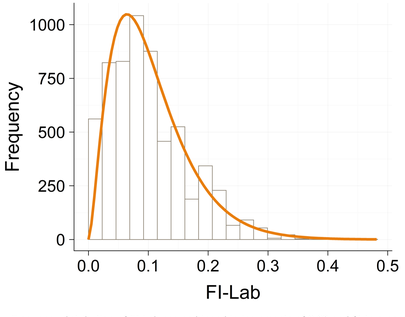
Table 2. Laboratory data used to construct FI-Labs.

Category	Test	# subjects	# studies	Units	Normal range*	% abnormal
Blood	Alanine Aminotransferase	6343	23	IU/L	1-44	3.9%
Blood	Albumin	4843	20	g/L	32-50	2.1%
Blood	Alkaline Phosphatase	6094	21	IU/L	31-121	4.6%
Blood	Aspartate Aminotransferase	6337	23	IU/L	1-37	3.4%
Blood	Basophils	4353	13	10^9/L	0-0.2	0.3%
Blood	Bilirubin	3657	17	mg/dL	0.2-1.2	2.9%
Blood	Bilirubin, Direct	2011	5	umol/L	0-6	4.3%
Blood	Bilirubin, Indirect	2686	6	umol/L	1.7-21	2.8%
Blood	Calcium	4738	19	mmol/L	2.1-2.6	5.5%
Blood	Chloride	4535	18	mmol/L	95-111	4%
Blood	Cholesterol	5184	18	mmol/L	0-5.7	41.5%
Blood	Creatine Kinase	5537	18	IU/L	0-190	8.6%
Blood	Creatinine	6344	23	umol/L	35-115	13.2%
Blood	Creatinine Clearance	2362	5	mL/min	>64	57.7%
Blood	Eosinophils	4353	13	10^9/L	0-0.55	5.6%
Blood	Erythrocytes	6002	21	10^12/L	4-5.5	14.3%
Blood	Folate	2937	13	nmol/L	6.8-45.1	40%
Blood	Gamma Glutamyl Transferase	3522	8	IU/L	6-50	8.5%
Blood	Glucose	6101	21	mmol/L	3.85-6.9	15.2%
Blood	Hematocrit	6000	21	%	35-49	7.1%
Blood	Hemoglobin	6307	23	g/L	120-161	10.2%
Blood	Hemoglobin A1c	3148	16	%	4-6	17.9%
Blood	Leukocytes	6307	23	10^9/L	4-11	4.9%
Blood	Lymphocytes	4353	13	10^9/L	1.02-4	15.5%
Blood	Mean Corpuscular Hemoglobin	3221	13	pg	27-34	3.5%
Blood	Mean Corpuscular Volume	3387	14	fL	80-101	3.7%
Blood	Monocytes	4353	13	10^9/L	0.2-1	4.5%
Blood	Neutrophils	4353	13	10^9/L	1.8-8	3.1%
Blood	Percent Basophils	3960	17	%	0-2	2.2%
Blood	Percent Eosinophils	3960	17	%	0-6.8	4.1%
Blood	Percent Lymphocytes	3960	17	%	15.5-46.6	9.5%
Blood	Percent Monocytes	3960	17	%	2.1-11.7	4.4%
Blood	Percent Neutrophils	3958	17	%	40.5-75	9.4%
Blood	Phosphate	3136	12	mmol/L	0.736-1.45	3.5%
Blood	Platelets	6268	23	10^9/L	140-420	4%
Blood	Potassium	6201	22	mmol/L	3.5-5.4	3.3%
Blood	Protein	4535	18	g/L	60-81	2.4%
Blood	Sodium	5883	21	mmol/L	135-147	4.1%
Blood	Thyrotropin	4878	21	mIU/L	0.4-5	7.8%
Blood	Triglycerides	3751	9	mmol/L	0.65-2.32	21.8%
Blood	Urea	4818	20	mmol/L	2.3-10.4	7%
Blood	Vitamin B12	4701	20	pmol/L	148-812	8.3%
Urine	Erythrocytes	2193	13	/HPF, /uL	Negative-Trace	10.4%
Urine	Glucose	3213	15	mg/dL	Negative-Trace	2.9%
Urine	Ketones	2570	13	mg/dL	Negative	3%
Urine	Lactate Dehydrogenase	3531	15	IU/L	77-270	2.6%
Urine	pH	2569	13		5-8	0.4%
Urine	Protein	3218	15	mg/dL	Negative-Trace	5.4%
Urine	Specific Gravity	2569	13	ratio	1.001-1.035	6.2%
Vital Sign	Diastolic Blood Pressure	6319	23	mmHg	60-90	6.4%
Vital Sign	Heart Rate	6315	23	beats/min	60-100	13.8%
Vital Sign	Pulse Pressure	6319	23	mmHg	30-60	36.7%
Vital Sign	Respiratory Rate	2278	10	breaths/min	12-30	1.1%
Vital Sign	Systolic Blood Pressure	6319	23	mmHg	90-140	29%
Vital Sign	Temperature	2443	12	C	36.1-37.2	17.4%

* For numeric normal ranges, there were often many different normal ranges for different studies, sites and subject characteristics. The low and high cutoff values shown here are the medians of their respective values.

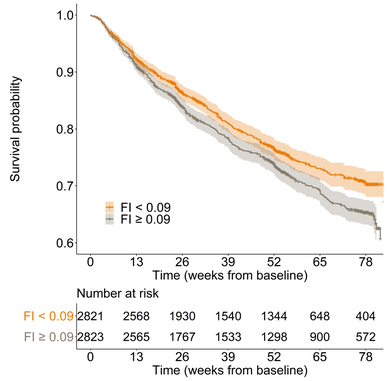
Results

Figure 1. FI-Lab score distribution.



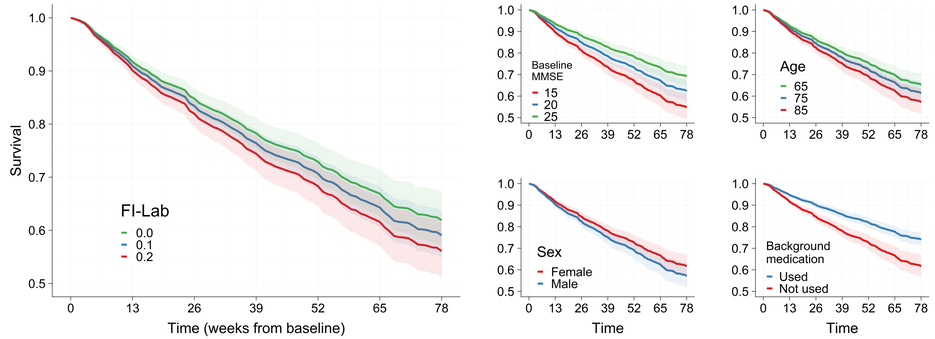
Frequency distribution of FI-Lab scores binned in increments of 0.02 and fit to a gamma distribution. Mean ± SD = 0.10 ± 0.07. The distribution is skewed with a long right tail and differs significantly from a normal distribution (Shapiro-Wilk test: p <0.001).

Figure 2. Kaplan-Meier survival curves, stratified by the median FI-Lab score of 0.08.



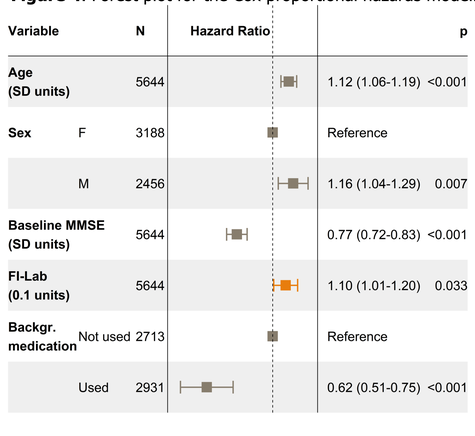
Survival curves are shown with 95% CI bands for the different strata.
The distributions were significantly different by the log-rank test (p<0.001).

Figure 3. Predicted survival curves for each predictor of the proportional hazards model, keeping other covariates constant.



Survival curves are shown with 95% CIs. Covariates were held constant as follows: FI-Lab = 0.09 (median), Baseline MMSE = 19.5 (mean), Age = 74 (mean), Sex = Female, Background medication = Not Used.

Figure 4. Forest plot for the Cox proportional hazards model.



Coefficient point estimates are presented with 95% CIs.
Continuous variables were re-scaled for interpretability: age and baseline MMSE were standardized to z-scores (mean = 0, SD = 1), while FI-Lab scores were multiplied by 10.

Discussion and Conclusions

- Individuals in the high frailty group were more likely to drop out (p=0.002), **Figure 2**.
- A Cox proportional hazards model, with study ID as a random effect, revealed significant associations in each predictor (**Figure 3, 4**):
  - A 0.1 increase in **FI-Lab** increased risk of dropout, HR = 1.10 (95% CI = 1.01-1.20).
  - One SD increase in **Age** (approximately 8.6 years) increased risk of dropout, HR = 1.12 (1.06-1.19).
  - **Males** were more likely to drop out, HR = 1.15 (1.03-1.29).
  - One SD increase in **baseline MMSE** (better cognition; ~5 points) decreased risk of dropout, HR = 0.77 (0.71-0.83).
  - Subjects who continued to **use background dementia medication** were less likely to drop out, HR = 0.62 (0.51-0.75).
- Frailty index scores based on lab and vital sign deficits from CAMD safety data were associated with subject dropout. Age, sex, baseline MMSE and dementia medication use were similarly or more strongly related to dropout, which suggests that there is limited value in excluding frail patients from dementia drug trials.

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ABBREVIATIONS
CI: Confidence Interval
CAMD: Coalition Against Major Diseases
FI: Frailty Index
MMSE: Mini-Mental State Examination
SD: Standard Deviation

REFERENCES
[1]Howlett, S. E., Rockwood, M. R., Mitnitski, A., & Rockwood, K. (2014). Standard laboratory tests to identify older adults at increased risk of death. *BMC Medicine, 12,* 171.
[2]Neville, J., Kopko, S., Broadbent, S., Avilés, *et al.* (2015). Development of a unified clinical trial database for Alzheimer's disease. *Alzheimer's & Dementia,* 11(10), 1212-1221.