A Frailty Index Based on Routinely Collected Laboratory Safety Data Predicts Adverse Events in a Sex-Specific Manner in Clinical Trials

Taylor Dunn MSc[1], Justin Stanley BScE[1], Susan E Howlett PhD[1,2], Arnold B Mitnitski PhD[1,2], Kenneth Rockwood MD[1,2]
[1]DGI Clinical Inc., Halifax, NS, Canada; [2]Dalhousie University, Halifax, NS, Canada

Background

Frailty is most commonly 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 objectives in this exploratory analysis were to:
1. Investigate the relationship between FI-Lab and adverse events (AE).
2. Explore sex differences in FI-Lab scores.

Methods

Design and Subjects
- The CAMD database consists of control arm pooled and standardized data from 24 trials for Alzheimer's disease with 6500 subjects. Of these, 23 studies (6278 subjects) reported lab test data. Many of the 200+ unique tests (blood, urine, vital sign measurements) in the database are rarely reported. To construct the FI-Lab, we excluded less common measures (here, if <2000 subjects had such a test). This yielded 60 total unique lab tests across the 23 studies (Table 2).
- Seven studies (with 1838 subjects) also reported adverse events with a severity rating of Mild, Moderate or Severe.

Frailty Index construction
- The FI-Lab was constructed for each subject using all of their available lab tests taken at screening (20-50 items; median 40).
- Each item was scored as 0 or 1 for normal or abnormal measurements. Normal ranges for each lab test were generally included in the data and missing values were imputed where possible. These normal ranges varied between and within studies (e.g. different values by sex and age).

Table 1. Demographics and FI-Lab characteristics of the 23 trials.

Study ID	Number of subjects	% female	Age, median (range)*	FI-Lab, # distinct items	FI-Lab, mean (SD)	# AE per subject, median (range)
1000	102	58.8%	76 (55-89)	39	0.10 (0.05)	
1009	164	55.5%	75 (60-86)	36	0.07 (0.06)	
1013	715	50.2%	76 (51-90+)	28	0.14 (0.08)	
1014	641	56.5%	76 (50-90+)	28	0.14 (0.08)	
1055	134	56.7%	75 (45-87)	23	0.09 (0.06)	2 (0-12)
1056	493	55.8%	73 (52-90+)	46	0.07 (0.05)	1 (0-13)
1057	500	61.4%	76 (50-90+)	46	0.07 (0.05)	1 (0-20)
1058	166	59.0%	73 (50-88)	46	0.07 (0.06)	0 (0-8)
1105	279	50.2%	74 (50-90+)	38	0.10 (0.05)	3 (0-24)
1107	144	61.1%	75 (48-89)	53	0.07 (0.04)	
1131	56	58.9%	77 (52-90+)	45	0.10 (0.04)	
1132	412	43.4%	72 (45-90+)	45	0.10 (0.05)	
1133	160	61.2%	74 (56-88)	47	0.06 (0.04)	
1134	105	81.9%	88 (65-90+)	46	0.08 (0.05)	
1135	268	55.2%	71 (50-89)	48	0.07 (0.04)	
1136	144	59.4%	74 (51-88)	33	0.12 (0.07)	
1137	215	50.7%	77 (54-90+)	43	0.12 (0.06)	
1138	202	57.4%	78 (51-90+)	45	0.13 (0.06)	
1139	167	67.7%	80 (50-90+)	46	0.15 (0.07)	
1141	487	55.4%	70 (50-90+)	40	0.09 (0.05)	4 (0-41)
1142	407	56.3%	78 (54-90+)	50	0.07 (0.04)	4 (0-34)
1143	103	83.5%	81 (59-90+)	25	0.18 (0.09)	
1144	214	64.5%	76 (50-90+)	46	0.06 (0.05)	
All	6278	56.5%	75 (45-90+)	60	0.10 (0.07)	2 (0-41)

* Ages above 89 are anonymized in the CAMD database.

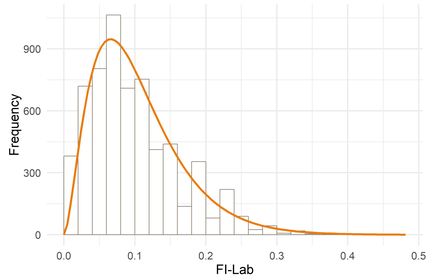
Table 2. Laboratory data used to construct FI-Labs.

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 Hb Concentration	3387	14	g/L	315-360	3.2%
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.

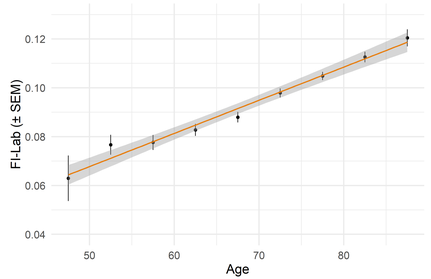
Results

Figure 1. FI-Lab score distribution.



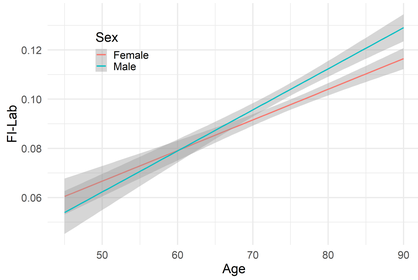
Frequency distribution of FI-Lab scores is shown in intervals of 0.02 and fit to a gamma distribution. Mean ± SD = 0.10 ± 0.06. The distribution is skewed with a long right tail, and differs significantly from a normal distribution (Shapiro-Wilk test: p <0.001).

Figure 2. The FI-Lab correlated significantly with age.



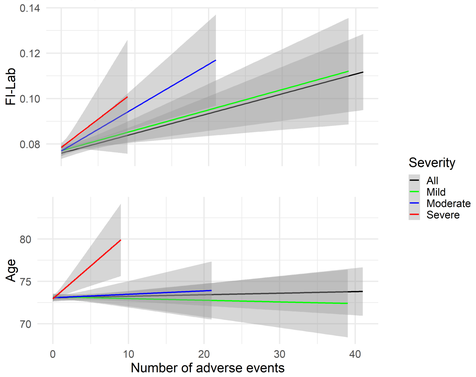
FI-Lab scores were binned by Age in 5 years intervals. The mean ± SEM scores for each interval are plotted against age. Data were fit with linear regression (r=0.18, p<0.001), and shown with the 95% CI band.

Figure 3. FI-Lab values were higher in older males.



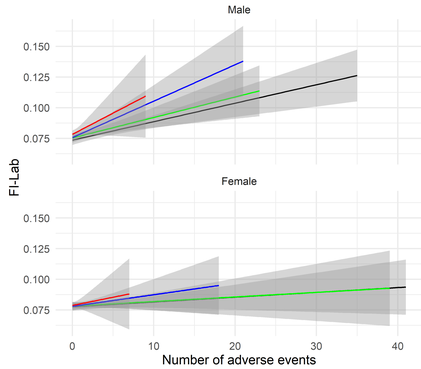
The best fit lines of FI-Lab versus age are shown with 95% CI by sex. Data were fit by linear regression (Females: r=0.17, p<0.001; Males: r=0.21; p<0.001). After age 60, mean FI-Lab scores were higher in males (t=2.46, p<0.05).

Figure 4. The FI-Lab correlated significantly with the number and severity of adverse events. Age correlated significantly only with the number of severe AEs.



The best fit lines of number of adverse events versus FI-Lab and Age are shown with 95% CI for the different AE severities. Data were fit by multiple Poisson regression with FI-Lab and Age as predictors of all AEs. FI-Lab: B=1.9, p<0.001; Age: B=-0.0001, p=0.9.

Figure 5. The FI-Lab predicts adverse events in males.



The best fit lines of number of adverse events versus FI-Lab are shown with 95% CI by severity of adverse events. Data were fit by Poisson regression. Females: all relationships were insignificant; Males: all relationships were significant at p<0.05.

Discussion and Next Steps

- Frailty index scores based on lab and vital sign **deficits from CAMD safety data** were correlated with subject age, as expected.
- FI-Lab scores were higher in males, driven by a crossover at age ~60 years. These findings contrast with the morbidity-mortality paradox seen with clinically-derived FI scores in community samples. There, females have higher mean FI scores, but lower FI lethality. Our data support the hypotheses that cellular and sub-cellular deficits scale up to promote frailty at the organ/organism levels and that males are more susceptible to their adverse effects, including dementia risk and disease expression.
- In males, the FI-Lab was a significant predictor of adverse events (all severities). By contrast, age was not a significant predictor (except for severe AEs).
- **Future work** will explore how the choice of items in the FI-Lab influences sex differences. Also, the effect of FI-Lab on longitudinal test scores (e.g. ADAS-Cog, ADCS-ADL) will be examined.

CONTACT posters@dgiclinical.com

ABBREVIATIONS
AEs: Adverse Events
CI: Confidence Interval
CAMD: Coalition Against Major Diseases
FI: Frailty Index
SEM: Standard Error of the Mean

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.