A procedure to create a frailty index using routinely-collected laboratory and clinical safety data from an Alzheimer disease clinical trial

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Background & Objectives:

- Most individuals with dementia are aged 75+ years and many are frail.
- Even so, most dementia clinical trials exclude older adults, making generalizability of treatment effects uncertain.
- We previously showed that frailty can be quantified with a frailty index (FI) based on accumulation of deficits in health and can even be constructed from hospital blood work.[1]
- Our objective was to determine whether we could construct FIs based on laboratory and clinical safety data from the double blind Video Imaging Synthesis of Treating Alzheimer's disease (VISTA) galantamine trial.

Methods & Analysis:

- VISTA was a 32-week, multi-centre trial of 130 community-dwelling subjects with mild-to-moderate Alzheimer disease (AD).
- Using validated procedures,[1] three FIs were constructed:
  1) FI-Clinical was based on 34 co-morbidities, physical deficits plus neurological function data.
  2) FI-Lab was constructed from 33 standard laboratory tests (e.g. red cell, white cell & platelet counts, liver, kidney & thyroid function).
  3) FI-Combined was created from all 67 items.
- For determining deficits, each results within the normal range were scored as 0; values outside the normal range were scored as 1. Items were summed and divided by the number measured (e.g. 34, 33, or 67) to yield an FI between 0-1.
- None of the items came from an outcome measure.

Table 1. Clinical data used to construct the FI-Clinical

Clinical category	Prevalence (%)[a]
Physical system	
Abdomen	10.7
Chest lungs	10.8
Ears nose throat	10.8
Extremities	17.7
Eyes	13.8
General appearance	8.5
Head neck	3.1
Heart	20.8
Musculoskeletal	23.8
Skin	10
Other	3.8
Neurological system	
Coordination	6.2
Cranial nerves	5.4
Gait	14.6
Muscle strength / movement	5.4
Sensory system	10.8
Tendon reflexes	13.1
Neurological signs	
Extrapyramidal signs	13.1
Myoclonus	1.5
Pyramidal signs	3.8
Disease status	
Allergic	18.5
Cardiovascular	65.4
Dermatological	26.9
Ears nose throat	36.9
Endocrine metabolic	40.8
Eyes	54.6
Gastrointestinal	62.3
Genito-urinary	64.6
Hematological	21.5
Musculoskeletal	70
Neurological	33.1
Psychiatric	28.5
Respiratory	17.7
Other, specify	29.2

Normal results were scored as 0 and abnormal results were scored as 1.[a]Percent of subjects with a deficit or who were scored as 1.

Table 2. Laboratory data used to construct the FI-Lab

Variable[a]	Low cut-off[d]	High cut-off[d]	Prevalence (%)[e]
Alkaline phosphatase (IU/L)	20	130	7
Alanine aminotransferase (U/L)	4	36	1.6
Aspartate aminotransferase (IU/L)	8	33	3.9
Vitamin B12 (pg/L)	118	701	4.7
Calcium (Mm)	2.3	2.7	36.4
Cholesterol (Mm)[b]	0	5.2	58.9
Creatine kinase (U/L)	55 (30)	170 (135)	18.6
Chloride (Mm)	95	103	44.2
Creatinine (µM)	53	106	28.7
Eosinophils (10**9/L)	0	0.45	5.7
Folate (nM)	11	57	10.1
Gamma-glutamyl transferase (U/L)	5	40	11.6
Glucose, random mM)[c]	3.8	11.1	4.7
Hemoglobin ((g/L)2)	135	180	51.6
Hematocrit (L/L)	0.4 (0.38)	0.54 (0.47)	29
Mean corpuscular hemoglobin (pg)	27	31	37.9
Mean corpuscular volume (fL)	80	96	21.8
Platelet (10**9/L)	150	450	4
Red blood cells (10**12/L)	4.6 (4.2)	6.2 (5.4)	51.6
Red blood cell distribution width (%)[c]	11.5	14.5	27.4
White blood cells (10**9/L)	4.5	11	9.4
Potassium (mM)	3.8	5	19.4
Lactate dehydrogenase (U/L)	100	190	17.8
Absolute lymphocytes count (10**9/L)	1	4.8	14.8
Absolute monocytes count (10**9/L)	0	0.8	4.7
Sodium (mM)	136	142	20.2
Absolute neutrophils count (10**9/L)	1.8	7.8	5.5
Total bilirubin (uM)	2	21	1.6
Total protein (g/L)	60	78	14.7
Thyroid stimulating hormone (µIU/L)	0.5	5	8.5
Uric acid (uM)	240 (160)	510 (430)	11.6
Urea (mM)	2.9	8.2	20.2
Urine specific gravity	1.016	1.022	78.3

Normal results were scored as 0 and abnormal results were scored as 1. [a]Normal reference values for blood work were from Henry[2] unless otherwise indicated. [b]Normal reference values from Stats Canada.[3] [c]Normal reference values from Objectives for the Qualifying Examination - Medical Council of Canada.[4] [d]For normal reference values that differed between the sexes, the low and high cut-offs are indicated ( ). [e]Percent of subjects with a deficit or who were scored as 1.

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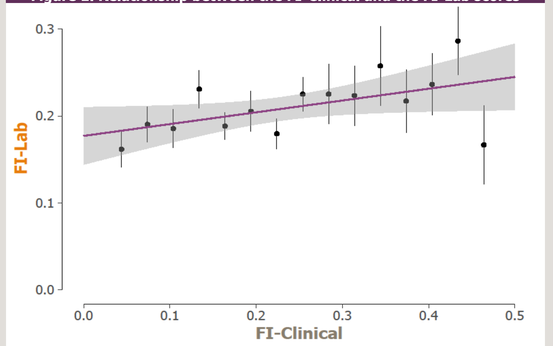
Table 3. Baseline demographic characteristics by grades of frailty

Characteristics	Grades of the FI				
FI-Clinical	**< 0.12**	**0.12 to 0.19**	**0.20 to 0.27**	**0.28 to 0.35**	**> 0.35**
N	22	30	40	21	17
Age (mean ± SD)	72.5 ± 8.2	76.1 ± 6.1	77.0 ± 7.8	79.6 ± 6.6	82.6 ± 7.3
FI (mean ± SD)	0.095 ± 0.025	0.157 ± 0.017	0.235 ± 0.025	0.311 ± 0.020	0.413 ± 0.030
Women (%)	63.6	56.7	60.0	71.4	70.6
ADAS-Cog (mean ± SD)	24.8 ± 7.5	26.3 ± 8.9	25.4 ± 7.0	27.7 ± 7.5	24.1 ± 6.6
MMSE (mean ± SD)	21.0 ± 4.1	21.0 ± 3.6	20.0 ± 3.7	20.5 ± 3.5	18.9 ± 4.1
FI-Lab	**< 0.12**	**0.12 to 0.19**	**0.20 to 0.27**	**0.28 to 0.35**	**> 0.35**
N	11	48	46	20	4
Age (mean ± SD)	76.1 ± 6.4	75.7 ± 9.5	77.8 ± 6.4	81.0 ± 5.9	73.0 ± 4.7
FI (mean ± SD)	0.080 ± 0.015	0.153 ± 0.026	0.234 ± 0.022	0.319 ± 0.022	0.371 ± 0.015
Women (%)	54.5	75.0	65.2	40.0	50.0
ADAS-Cog (mean ± SD)	25.4 ± 9.2	26.0 ± 8.0	25.3 ± 7.4	26.0 ± 7.4	28.0 ± 5.4
MMSE (mean ± SD)	19.5 ± 2.7	20.3 ± 3.6	20.2 ± 4.2	21.3 ± 3.9	19.0 ± 4.1
FI-Combined	**< 0.12**	**0.12 to 0.19**	**0.20 to 0.27**	**0.28 to 0.35**	**> 0.35**
N	10	44	47	26	3
Age (mean ± SD)	71.4 ± 8.7	75.3 ± 7.4	77.7 ± 7.3	81.2 ± 6.9	82.7 ± 3.2
FI (mean ± SD)	0.108 ± 0.015	0.166 ± 0.021	0.227 ± 0.020	0.316 ± 0.020	0.385 ± 0.011
Women (%)	60.0	65.9	59.6	69.2	33.3
ADAS-Cog (mean ± SD)	23.9 ± 8.2	26.6 ± 8.4	25.5 ± 7.4	25.2 ± 6.9	28.0 ± 3.0
MMSE (mean ± SD)	22.0 ± 2.9	20.1 ± 4.1	20.4 ± 3.5	20.1 ± 3.7	18.7 ± 6.7

Figure 1. Relationship between the FI-Clinical and the FI-Lab scores

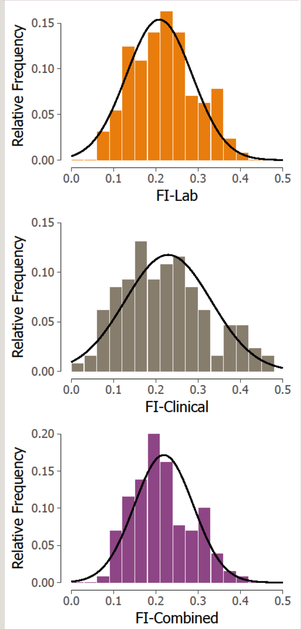


The FI-Clinical scores were pooled and the means (± SEM) are shown in increments of 0.03. The FI-Lab increased with FI-Clinical scores ($p < 0.05$). The data were fit with a linear regression, resulting in a correlation coefficient of $r = 0.5809$. The band around the best fit line represents the 95% confidence interval of the estimated fit parameters. SEM, standard error of the mean.

Discussion & Conclusions:

- These data demonstrate that:
  1) An FI score can be constructed based on existing laboratory and/or clinical data that are routinely collected as safety data in the Alzheimer drug trials.
  2) Older individuals with a wide range of FI scores are recruited in drug trials, despite efforts to exclude them.
- Failure to consider varying frailty levels in drug trial participants is a missed opportunity to determine whether drugs work in patients who are most likely to take them.

Figure 2. Frequency distribution for the FI-Clinical, FI-Lab and FI-Combined



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