

Validity and performance of blood biomarkers for Alzheimer's disease to predict dementia risk in a large clinic-based cohort

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Supplementary Tables

	Male gender (n=871)		Female gender (n=1406)		p-value
Biological biomarkers					
CSF NfL, pg/mL, median, (Q1-Q3)	1290	(932; 2030)	1200	(818; 1850)	0.085
CSF Aβ42/40 ratio (x100), median, (Q1-Q3)	8.4	(5.5; 10.8)	8.1	(5.3; 11.0)	0.66
CSF total Tau, pg/mL, median, (Q1-Q3)	292	(204; 432)	297	(223; 474)	0.24
CSF p181-Tau, pg/mL, median, (Q1-Q3)	52.6	(42.1; 69.8)	57.2	(47.2; 77.0)	0.017
Blood NfL, , pg/mL, median, (Q1-Q3)	18	(13.3; 25.0)	18.3	(13.4; 25.1)	0.46
Blood Aβ42/40 ratio, (x100), median, (Q1-Q3)	5.6	(4.7; 6.4)	5.7	(4.9; 6.6)	0.015
Blood total Tau, pg/mL, median, (Q1-Q3)	1.7	(1.3; 2.5)	1.9	(1.5; 2.7)	<10 ⁻⁴
Blood p181-Tau, pg/mL, median, (Q1-Q3)	0.9	(0.6; 1.5)	0.9	(0.6; 1.3)	0.089

Suppl. Table 1. Gender differences in CSF and blood biomarkers concentrations.
Variables are represented with median and 1st and 3rd interquartiles (Q1-Q3).

Biomarker	Tertile of distribution	Blood			CSF		
		Concentration range	AD dementia converters (n=64)	Incidence rate per 100PYFU [95%CI]	Concentration range	AD dementia converters (n=64)	Incidence rate per 100PYFU [95%CI]
p181-tau	low	0.34-0.70	9	1.96 [0.90; 3.73]	14.6-47.6	4	0.76 [0.21; 1.94]
	intermediate	0.71-1.12	13	2.76 [1.47; 4.71]	47.8-66.3	11	2.18 [1.09; 3.91]
	high	1.16-5.38	42	11.51 [8.30;15.56]	66.7-261.5	49	11.87 [8.78;15.69]
NfL	low	4.3-14.9	14	2.16 [1.18; 3.63]	284-993	5	1.00 [0.32; 2.33]
	intermediate	15.0-22.2	19	3.84 [2.31; 5.99]	1000-1680	13	2.63 [1.40; 4.50]
	high	22.5-100	31	10.06 [6.84;14.29]	1700-11800	41	11.44 [8.21;15.52]
A β 42/40 ratio	low	1.33-5.09	33	7.02 [4.83; 9.86]	2.29-6.22	49	12.31 [9.10;16.27]
	intermediate	5.11-6.18	18	4.31 [2.55; 6.80]	6.25-10.17	12	2.45 [1.27; 4.28]
	high	6.19-19.32	12	2.37 [1.23; 4.14]	10.2-18.9	1	0.19 [0.00; 1.06]
Total tau	low	0.42-1.55	18	3.67 [2.17; 5.80]	86-234	3	0.58 [0.12; 1.68]
	intermediate	1.56-2.28	22	4.48 [2.81; 6.78]	236-386	10	1.95 [0.94; 3.59]
	high	2.29-18.4	23	5.58 [3.54; 8.38]	388-2000	51	12.60 [9.38;16.56]

Suppl. Table 2. Incidence rates of AD dementia based on blood and CSF biomarkers concentrations in the CSF sub-sample (n=357). A β : Amyloid Beta, AD: Alzheimer's disease, CI: confidence interval, NfL: Neurofilaments Light chain, PYFU: Person-years of follow-up. Ranges of concentrations are in pg/mL, except for A β 42/40 ratio.

	c Index [95%CI]	Brier Score [95%CI]	c Index difference [95%CI]
<i>Clinical setting + Scheltens scale</i>			
Reference model: age, gender, education, memory, executive functions, <u>visual scale for hippocampal atrophy</u>	0.905 [0.887;0.923]	0.072 [0.071;0.072]	Ref
Ref model + NfL	0.905 [0.888;0.923]	0.072 [0.071;0.072]	0.000 [-.001;0.002]
Ref model + A β 42/40 ratio	0.908 [0.890;0.926]	0.070 [0.070;0.070]	0.003 [-.003;0.009]
Ref model + p181-tau	0.916 [0.901;0.930]	0.067 [0.067;0.068]	0.011 [0.003;0.019]
Ref model + total-tau	0.905 [0.887;0.924]	0.071 [0.071;0.072]	0.000 [-.002;0.003]
Ref model + Best combination (p181-tau + A β 42/40 ratio)	0.917 [0.903;0.932]	0.066 [0.066;0.066]	0.012 [0.002;0.022]

Suppl. Table 3. Performance for predicting AD dementia during a 5-year follow-up when adding the visual scale for hippocampal atrophy (Scheltens scale) to the “clinical” reference model.

	CDR at 0			CDR at 0.5		
	c Index [95%CI]	Brier Score [95%CI]	c Index difference [95%CI]	c Index [95%CI]	Brier Score [95%CI]	c Index difference [95%CI]
Blood biomarkers alone						
NfL	0.661 [0.559;0.763]	0.031 [0.030;0.031]	-0.189 [-0.309;-0.068]	0.650 [0.608;0.692]	0.147 [0.147;0.148]	-0.074 [-0.107;-0.041]
A β 42/40 ratio	0.673 [0.587;0.758]	0.031 [0.031;0.031]	-0.170 [-0.288;-0.051]	0.596 [0.555;0.637]	0.149 [0.148;0.149]	-0.126 [-0.165;-0.086]
pTau181	0.830 [0.694;0.967]	0.029 [0.029;0.029]	-0.018 [-0.056;0.020]	0.697 [0.658;0.737]	0.139 [0.139;0.140]	-0.024 [-0.043;-0.005]
total-tau	0.452 [0.324;0.580]	0.030 [0.030;0.030]	-0.396 [-0.560;-0.233]	0.520 [0.477;0.564]	0.151 [0.151;0.152]	-0.201 [-0.244;-0.157]
Best combination: NfL + p181-tau + A β 42/40 ratio	0.847 [0.742;0.953]	0.028 [0.028;0.029]	Ref	0.722 [0.687;0.757]	0.137 [0.137;0.138]	Ref
Clinical setting						
Reference model: age, gender, education, memory, executive functions	0.849 [0.773;0.925]	0.030 [0.029;0.030]	Ref	0.861 [0.837;0.885]	0.108 [0.107;0.108]	Ref
Ref model + NfL	0.856 [0.789;0.924]	0.030 [0.030;0.031]	0.007 [-0.013;0.026]	0.861 [0.837;0.885]	0.109 [0.108;0.109]	-0.000 [-0.002;0.002]
Ref model + A β 42/40 ratio	0.886 [0.826;0.946]	0.032 [0.032;0.032]	0.037 [-0.017;0.091]	0.864 [0.840;0.888]	0.106 [0.106;0.106]	0.003 [-0.003;0.008]
Ref model + p181-tau	0.872 [0.797;0.947]	0.026 [0.026;0.026]	0.024 [-0.034;0.083]	0.869 [0.847;0.890]	0.104 [0.104;0.104]	0.007 [0.000;0.015]
Ref model + total-tau	0.840 [0.760;0.920]	0.030 [0.030;0.031]	-0.011 [-0.024;0.002]	0.862 [0.838;0.886]	0.107 [0.107;0.108]	0.001 [-0.001;0.003]
Ref model + Best combination (p181-tau + A β 42/40 ratio)	0.894 [0.835;0.953]	0.027 [0.027;0.028]	0.046 [-0.027;0.118]	0.870 [0.848;0.891]	0.103 [0.103;0.104]	0.009 [-0.000;0.017]
Research setting						
Reference model: age, gender, education, memory, executive functions, ApoE genotype, quantitative MRI	0.855 [0.776;0.934]	0.031 [0.030;0.031]	Ref	0.884 [0.861;0.907]	0.097 [0.096;0.097]	Ref
Ref model + NfL	0.864 [0.789;0.938]	0.030 [0.030;0.031]	0.009 [-0.020;0.037]	0.882 [0.859;0.906]	0.097 [0.097;0.098]	-0.002 [-0.003;-0.000]
Ref model + A β 42/40 ratio	0.886 [0.828;0.945]	0.030 [0.030;0.030]	0.032 [-0.024;0.088]	0.886 [0.863;0.910]	0.096 [0.095;0.096]	0.002 [-0.004;0.008]
Ref model + p181-tau	0.885 [0.815;0.955]	0.028 [0.028;0.029]	0.032 [-0.026;0.090]	0.888 [0.867;0.909]	0.094 [0.094;0.094]	0.004 [-0.002;0.009]
Ref model + total-tau	0.854 [0.777;0.932]	0.031 [0.031;0.031]	-0.000 [-0.009;0.009]	0.883 [0.859;0.906]	0.097 [0.097;0.097]	-0.002 [-0.004;0.001]
Ref model + Best combination (p181-tau + A β 42/40 ratio)	0.900 [0.829;0.971]	0.027 [0.027;0.027]	0.047 [-0.040;0.135]	0.888 [0.866;0.910]	0.094 [0.093;0.094]	0.004 [-0.004;0.011]

Suppl. Table 4. Performance for predicting AD dementia during a 5-year follow-up according to baseline clinical status (CDR=0 or CDR=0.5).

	Non amnesic MCI (n=659)			amnesic MCI (n=1061)		
	c Index [95%CI]	Brier Score [95%CI]	c Index difference [95%CI]	c Index [95%CI]	Brier Score [95%CI]	c Index difference [95%CI]
Blood biomarkers alone						
NfL	0.660 [0.564;0.756]	0.051 [0.051;0.052]	-0.112 [-.188;-.035]	0.665 [0.623;0.707]	0.158 [0.157;0.158]	-0.075 [-.108;-.042]
Aβ42/40 ratio	0.667 [0.572;0.762]	0.051 [0.051;0.052]	-0.104 [-.204;-.003]	0.619 [0.577;0.661]	0.156 [0.155;0.156]	-0.124 [-.167;-.082]
pTau181	0.712 [0.625;0.798]	0.050 [0.049;0.050]	-0.055 [-.101;-.009]	0.720 [0.679;0.760]	0.142 [0.141;0.142]	-0.019 [-.036;-.001]
total-tau	0.524 [0.424;0.623]	0.050 [0.050;0.051]	-0.243 [-.345;-.142]	0.503 [0.455;0.550]	0.160 [0.160;0.161]	-0.238 [-.289;-.186]
Best combination: NfL + p181-tau + Aβ42/40 ratio	0.767 [0.699;0.836]	0.050 [0.050;0.051]	Ref	0.739 [0.703;0.775]	0.140 [0.140;0.141]	Ref
Clinical setting						
Reference model: age, gender, education, memory, executive functions	0.807 [0.719;0.895]	0.053 [0.052;0.053]	Ref	0.859 [0.835;0.883]	0.113 [0.112;0.113]	Ref
Ref model + NfL	0.815 [0.739;0.892]	0.053 [0.052;0.053]	0.009 [-.016;0.034]	0.860 [0.837;0.884]	0.113 [0.112;0.113]	0.001 [-.001;0.003]
Ref model + Aβ42/40 ratio	0.819 [0.740;0.899]	0.053 [0.052;0.053]	0.013 [-.011;0.038]	0.865 [0.841;0.888]	0.110 [0.109;0.110]	0.005 [-.002;0.012]
Ref model + p181-tau	0.834 [0.767;0.901]	0.051 [0.050;0.051]	0.027 [-.011;0.066]	0.871 [0.850;0.892]	0.107 [0.107;0.108]	0.012 [0.003;0.021]
Ref model + total-tau	0.816 [0.739;0.893]	0.055 [0.054;0.055]	0.010 [-.011;0.031]	0.860 [0.836;0.884]	0.113 [0.112;0.113]	0.000 [-.001;0.002]
Ref model + Best combination (p181-tau + Aβ42/40 ratio)	0.846 [0.795;0.897]	0.051 [0.051;0.052]	0.040 [-.005;0.085]	0.873 [0.851;0.894]	0.105 [0.105;0.106]	0.014 [0.002;0.025]
Research setting						
Reference model: age, gender, education, memory, executive functions, ApoE genotype, quantitative MRI	0.811 [0.709;0.913]	0.055 [0.055;0.055]	Ref	0.883 [0.864;0.903]	0.101 [0.101;0.102]	Ref
Ref model + NfL	0.802 [0.701;0.904]	0.056 [0.056;0.057]	-0.009 [-.036;0.017]	0.882 [0.862;0.901]	0.102 [0.101;0.102]	-0.002 [-.003;-.000]
Ref model + Aβ42/40 ratio	0.827 [0.735;0.918]	0.057 [0.057;0.058]	0.016 [-.004;0.036]	0.886 [0.865;0.906]	0.100 [0.099;0.100]	0.003 [-.005;0.010]
Ref model + p181-tau	0.826 [0.739;0.914]	0.054 [0.054;0.055]	0.014 [-.009;0.037]	0.888 [0.869;0.907]	0.096 [0.095;0.096]	0.004 [-.002;0.011]
Ref model + total-tau	0.830 [0.743;0.918]	0.054 [0.054;0.055]	0.019 [-.004;0.042]	0.882 [0.862;0.902]	0.101 [0.101;0.102]	-0.001 [-.002;0.001]
Ref model + Best combination (p181-tau + Aβ42/40 ratio)	0.830 [0.748;0.912]	0.058 [0.057;0.058]	0.017 [-.021;0.055]	0.888 [0.868;0.908]	0.095 [0.095;0.096]	0.004 [-.005;0.014]

Suppl. Table 5. Performance for predicting AD dementia during a 5-year follow-up in amnesic MCI vs non-amnesic patients at baseline.

	c Index [95%CI]	Brier Score [95%CI]	c Index difference [95%CI]
<i>Blood biomarkers alone</i>			
NfL	0.659 [0.618;0.700]	0.104 [0.104;0.105]	-0.098 [-.132;-0.064]
A β 42/40 ratio	0.645 [0.606;0.683]	0.103 [0.103;0.103]	-.113 [-.149;-0.077]
pTau181	0.734 [0.694;0.774]	0.096 [0.096;0.096]	-.024 [-.042;-0.007]
total-tau	0.545 [0.503;0.588]	0.105 [0.104;0.105]	-.213 [-.262;-0.164]
Best combination: NfL + p181-tau + A β 42/40 ratio	0.758 [0.723;0.793]	0.095 [0.095;0.095]	Ref.
<i>Clinical setting</i>			
Reference model: age, gender, education, memory, executive functions	0.883 [0.859;0.907]	0.072 [0.071;0.072]	Ref.
Ref model + NfL	0.887 [0.864;0.909]	0.071 [0.071;0.072]	0.004 [0.001;0.007]
Ref model + A β 42/40 ratio	0.888 [0.866;0.911]	0.070 [0.070;0.071]	0.005 [-.003;0.013]
Ref model + p181-tau	0.896 [0.875;0.916]	0.068 [0.068;0.068]	0.012 [0.004;0.020]
Ref model + total-tau	0.884 [0.860;0.908]	0.072 [0.071;0.072]	0.000 [-.002;0.003]
Ref model + Best combination (p181-tau + A β 42/40 ratio)	0.899 [0.880;0.918]	0.067 [0.067;0.067]	0.015 [0.005;0.026]
<i>Research setting</i>			
Reference model: age, gender, education, memory, executive functions, ApoE genotype, quantitative MRI	0.908 [0.887;0.929]	0.064 [0.064;0.064]	Ref.
Ref model + NfL	0.908 [0.888;0.929]	0.064 [0.064;0.064]	0.000 [-.001;0.001]
Ref model + A β 42/40 ratio	0.915 [0.896;0.934]	0.063 [0.063;0.063]	0.007 [0.000;0.014]
Ref model + p181-tau	0.912 [0.894;0.931]	0.062 [0.062;0.062]	0.004 [-.002;0.011]
Ref model + total-tau	0.908 [0.888;0.929]	0.064 [0.064;0.064]	0.000 [-.002;0.003]
Ref model + Best combination (p181-tau + A β 42/40 ratio)	0.917 [0.899;0.935]	0.061 [0.061;0.061]	0.008 [-.001;0.018]

Suppl. Table 6. Performance for predicting AD dementia after exclusion of patients with chronic kidney disease (eGFR>60, n=2063).

	c Index [95%CI]	Brier Score [95%CI]	c Index difference [95%CI]
<i>Clinical setting</i>			
Reference model: age, gender, education, memory, executive functions, eGFR, History of cardiovascular event	0.884 [0.862;0.905]	0.076 [0.075;0.076]	Ref
Ref model + NfL	0.887 [0.866;0.907]	0.075 [0.075;0.076]	0.003 [0.000;0.005]
Ref model + A β 42/40 ratio	0.888 [0.868;0.909]	0.075 [0.074;0.075]	0.004 [-.002;0.011]
Ref model + p181-tau	0.898 [0.880;0.915]	0.071 [0.071;0.072]	0.014 [0.006;0.021]
Ref model + total-tau	0.885 [0.863;0.906]	0.076 [0.075;0.076]	0.001 [-.001;0.002]
Ref model + Best combination (p181-tau + A β 42/40 ratio)	0.900 [0.883;0.917]	0.071 [0.071;0.071]	0.016 [0.007;0.026]
<i>Research setting</i>			
Reference model: age, gender, education, memory, executive functions, GFR, History of cardiovascular event, ApoE genotype, quantitative MRI	0.907 [0.887;0.926]	0.067 [0.066;0.067]	Ref
Ref model + NfL	0.908 [0.889;0.927]	0.066 [0.066;0.067]	0.002 [0.000;0.003]
Ref model + A β 42/40 ratio	0.912 [0.894;0.931]	0.066 [0.066;0.066]	0.006 [0.000;0.011]
Ref model + p181-tau	0.913 [0.896;0.931]	0.064 [0.064;0.065]	0.007 [0.001;0.012]
Ref model + total-tau	0.906 [0.887;0.926]	0.066 [0.066;0.067]	-.000 [-.003;0.002]
Ref model + Best combination (p181-tau + A β 42/40 ratio)	0.917 [0.901;0.934]	0.064 [0.064;0.064]	0.010 [0.003;0.018]

Suppl. Table 7. Performance for predicting AD dementia during a 5-year follow-up after adjustment of “clinical” and “research” models on eGFR (estimated glomerular filtration rate) and history of cardiovascular event (myocardial infarction or stroke)