

Longitudinal clinical outcomes and blood biomarkers of inflammation and neurodegeneration in dementia with Lewy bodies

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Introduction

Longitudinal measurement of blood biomarkers in DLB may reveal important pathological processes or assist with diagnosis and prognostication. Biomarkers reflecting neuropathology include:

- Neurodegeneration: neurofilament light (NfL)
- Alzheimer’s disease (AD): phosphorylated tau-181 (p-tau181)
- Astrocyte activation: glial fibrillary acidic protein (GFAP), YKL-40 (aka CHI3L1)
- Inflammation: cytokines IL-1β, IL-4, IL-6, IL-8, TNF-α, IFN-γ, IL-10; however previous results have been inconsistent [1].

Aim

To describe associations between longitudinal clinical outcomes and blood biomarkers of neurodegeneration, inflammation and AD in DLB.

References

[1] Loveland 2023 IJMS; [2] McKeith 2017 Neurol; [3] Feizpour 2024 eBioMedicine. Figures were created with Biorender.com and Stata Statistical Software (18).

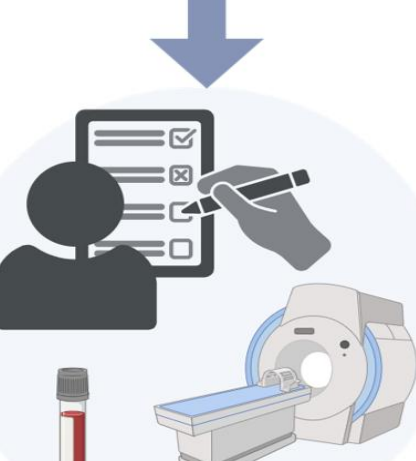
Methods

Figure 1. A longitudinal 3-year observational study of DLB

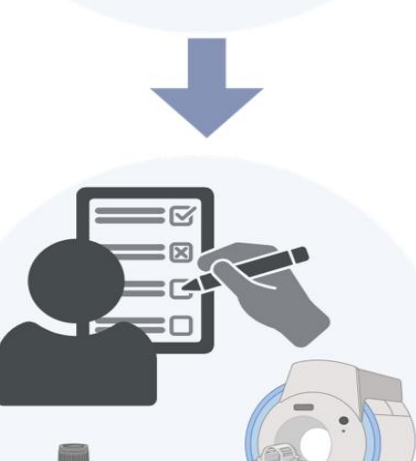
A. Recruitment



B. Baseline



C. 3 years



A. Community-dwelling people with probable DLB [2].

B. Clinical evaluation, neuro-imaging (18F-NAV4694 amyloidβ PET), fasting blood. Plasma analysis:

- Simoa: NfL, p-tau181, GFAP
- ELISA: YKL-40
- MesoScale Discovery: IL-6, IL-8, IL-10, IFN-γ.

C. Clinical outcomes at study completion included whether participants were deceased, living in a residential aged care facility (RACF), or community-dwelling.

Results

Clinical:

- At 3 years, death/RACF entry was associated with older age, visual hallucinations and AChEI medication (Table 1).
- Cognition (MMSE) was slightly worse and there was a signal towards higher frequency of APOE e4 carriers and amyloidβ(+) PET status.

Biomarkers:

- Higher baseline levels of p-tau181, GFAP and IL-6, and lower IL-10, were detected in the death/RACF group, particularly at the upper quartile (Table 2).
- There was a similar trend towards higher NfL in the deceased/RACF group.

	DLB n=28	3-year outcome	
		Community-dwelling, n=17	Death/RACF n=11
Age, years	73.4±5.7	72.2±6.2	75.3±4.7
Male sex, n (%)	24 (86%)	16 (94%)	8 (73%)
Years of education	13.4±3.5	14.2± 3.2	12.3±3.8
APOE e4 carrier, n (%)	15 (55%)	7 (41%)	8 (73%)
Amyloidβ(+) PET* Centiloid	15 (56%, n=27) 43.1 [8.3, 98.1]	8 (47%) 12.25 [2.3, 43.7]	7 (70%, n=10) 88.6 [24.7, 113.8]
Core DLB features			
Fluctuations, n (%)	26 (93%)	15 (88%)	11 (100%)
Visual hallucinations, n (%)	11 (39%)	4 (24%)	7 (64%)
Parkinsonism, n (%)	23 (82%)	13 (77%)	10 (91%)
RBD, n (%)	22 (79%)	15 (88%)	7 (64%)
AChEI medication, n (%)	16 (57%)	7 (41%)	9 (82%)
MMSE	26 [24, 27]	26 [26, 28]	25 [23, 26]
Clinical frailty scale	4 [4, 5]	4 [4, 5]	5 [4, 5]
UPDRS-III	17.5 [11, 27]	16 [11, 22]	21 [11, 30]
Geriatric depression scale	3 [1, 3]	3 [1, 6.5]	3 [2, 7]
NPI-12 symptom score	15 [5, 30]	20 [8, 31]	15 [4, 20]

Conclusions

In this longitudinal DLB cohort, death/RACF entry at 3 years was associated with:

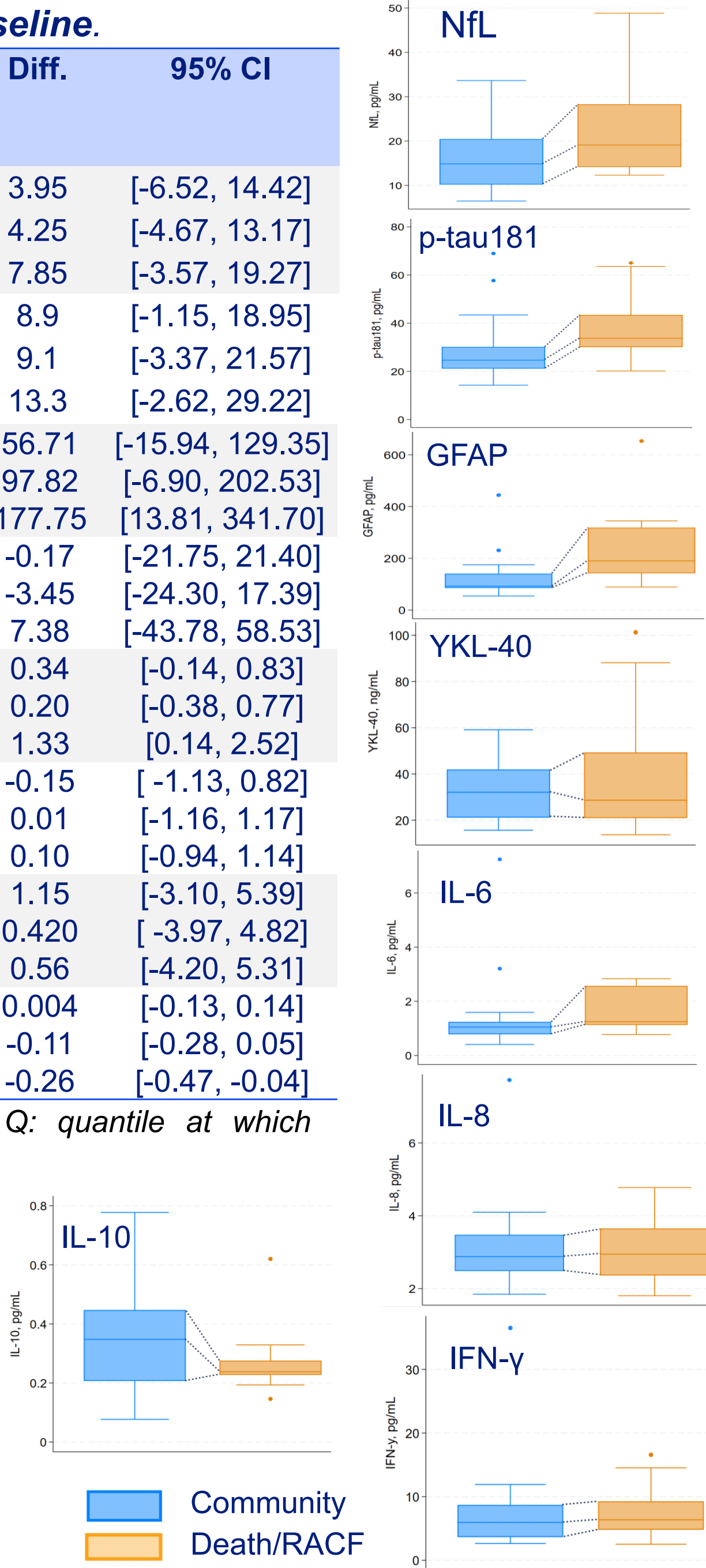
- Neuropsychiatric symptoms and amyloid neuropathology. This likely reflects a more severe disease trajectory, although older age and worse cognition may indicate a more advanced disease group at baseline.
- Higher levels of biomarkers connected to neurodegeneration (NfL), AD (p-tau181), astrocyte activation (GFAP) and a pro-inflammatory state (higher IL-6, lower IL-10).

Table 2. Plasma biomarkers at baseline.

	Q.	3-year outcome		Diff.	95% CI
		Community-dwelling, n=17	Death/RACF, n=11		
NfL, pg/mL	0.25	10.2	14.15	3.95	[-6.52, 14.42]
	0.5	14.85	19.10	4.25	[-4.67, 13.17]
	0.75	20.45	28.30	7.85	[-3.57, 19.27]
p-tau181, pg/mL	0.25	21.15	30.05	8.9	[-1.15, 18.95]
	0.5	24.65	33.75	9.1	[-3.37, 21.57]
	0.75	30.15	43.45	13.3	[-2.62, 29.22]
GFAP, pg/mL	0.25	85.40	142.10	56.71	[-15.94, 129.35]
	0.5	92.14	189.95	97.82	[-6.90, 202.53]
	0.75	140.70	318.45	177.75	[13.81, 341.70]
YKL-40, ng/mL	0.25	21.11	20.93	-0.17	[-21.75, 21.40]
	0.5	32.09	28.64	-3.45	[-24.30, 17.39]
	0.75	41.93	49.31	7.38	[-43.78, 58.53]
IL-6, pg/mL	0.25	0.78	1.12	0.34	[-0.14, 0.83]
	0.5	1.05	1.25	0.20	[-0.38, 0.77]
	0.75	1.24	2.60	1.33	[0.14, 2.52]
IL-8, pg/mL	0.25	2.51	2.36	-0.15	[-1.13, 0.82]
	0.5	2.94	2.95	0.01	[-1.16, 1.17]
	0.75	3.55	3.65	0.10	[-0.94, 1.14]
IFN-γ, pg/mL	0.25	3.65	4.79	1.15	[-3.10, 5.39]
	0.5	5.95	6.37	0.420	[-3.97, 4.82]
	0.75	8.70	9.26	0.56	[-4.20, 5.31]
IL-10, pg/mL	0.25	0.22	0.23	0.004	[-0.13, 0.14]
	0.5	0.35	0.24	-0.11	[-0.28, 0.05]
	0.75	0.53	0.28	-0.26	[-0.47, -0.04]

CI: confidence interval; Diff: difference; Q: quantile at which regression analysis was performed.

Data is frequency (%), mean±sd, or median [IQR1,IQR3]. AChEI: acetylcholinesterase inhibitor; MMSE: Mini-Mental State Examination; NPI: Neuropsychiatric Inventory; UPDRS-III: Unified Parkinson's Disease Rating Scale. *Amyloidβ(+) PET threshold ≥25 Centiloid [3].



Future directions:

- Larger cohort sizes and replication in longitudinal studies will address several of our study limitations.
- Exploration of longitudinal biomarker trajectories and their relationship with clinical outcomes.