On Gaps of Clinical Diagnosis of Dementia Subtypes: A Study of Alzheimer's Disease and Lewy Body Disease

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Introduction

- Early accurate clinical diagnosis for dementia subtypes is vital for clinical care and clinical trials.
- Clinical differentiation between Alzheimer's disease (AD), Lewy body disease (LBD) and the Lewy body variant of Alzheimer's disease (AD+LBD) could be difficult.
- How the magnitude of diagnostic uncertainty varies across dementia spectrums and demographic variables is unclear.
- Use postmortem autopsy-confirmed pathological results as the standard reference to assess the clinical subtype diagnosis quality across these factors.

Methods

- ***Cohort studied:*** retrospectively selected from the National Alzheimer's Coordinating Center (NACC) dataset.
- ***Statistical methods:*** bootstrapping methods with 1000 iterations for each Clinical Dementia Rating (CDR) stage 0.5, 1.0, 2.0 and 3.0.
- ***Evaluation time points and metrics: first*** visits at each CDR stage using precision (PPV), sensitivity and specificity.

Table 1: Definition of autopsy-confirmed results from NACC measurements

Dementia Subtype	AD	LBD	AD+LBD	Neither
Definition	NPADNC=2 or 3 and NACCLEWY=0	NPADNC=0 or 1 and NACCLEWY=3	NPADNC=2 or 3 and NACCLEWY=1,2, or 3	others

NPADNC: 0=Not AD, 1=Low ADNC, 2=Intermediate ADNC, 3=High ADNC
NACCLEWY: 0=No Lewy body pathology, 1=Brainstem-predominant, 2=Limbic (transitional) or amygdala-predominant, 3=Neocortical(diffuse).

Table 2: Definition of clinical diagnosis results from NACC measurements

Dementia Subtype	AD	LBD	AD+LBD	Neither
Definition	NACCALZD=1 and NACCLBDE=0	NACCALZD=0 and NACCLBDE=1	NACCALZD=1 and NACCLBDE=1	others

NACCALZD: 0=Cognitive impairment (dementia, MCI, or impaired, not MCI) and no AD. 1=Any cognitive impairment and AD etiologic diagnosis. 8=Normal cognition.
NACCLBDE: 0=Cognitive impairment and no LBD. 1=Any cognitive impairment and LBD etiologic diagnosis. 8=Normal cognition.

Table 3: Distribution of clinical diagnosis vs. autopsy results in CDR 0.5 to 3.0

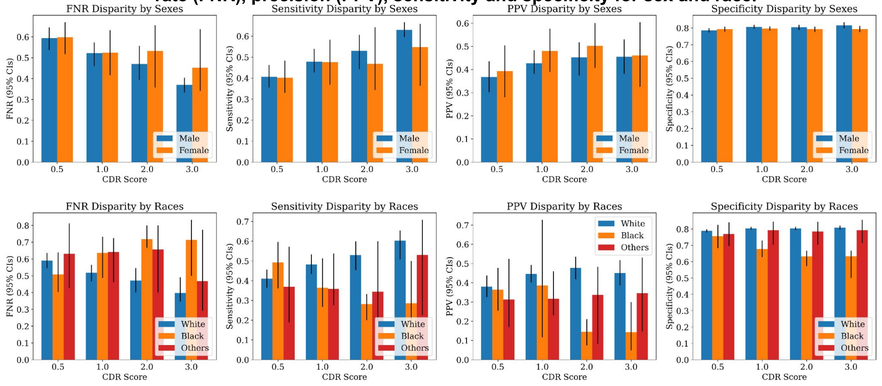
		Clinical Diagnosis				
Autopsy Results		**AD**	**LBD**	**AD+LBD**	**Neither**	**CDR**
	AD	288	8	9	202	0.5
	LBD	8	14	2	11	
	AD+LBD	200	26	9	91	
	Neither	114	15	4	242	
	AD	483	3	22	55	1.0
	LBD	6	12	7	1	
	AD+LBD	371	33	27	30	
	Neither	112	18	5	157	
	AD	315	6	11	25	2.0
	LBD	3	8	1	1	
	AD+LBD	252	14	18	14	
	Neither	49	16	4	78	
	AD	217	4	13	24	3.0
	LBD	1	7	0	0	
	AD+LBD	172	19	10	11	
	Neither	38	5	3	77	

Table 4: Clinical diagnosis performance (bootstrap median with 95% CIs)

Clinical Diagnosis	CDR	Precision (PPV)	Sensitivity	Specificity
AD	0.5	0.47 (0.43, 0.51)	0.57 (0.52, 0.61)	0.56 (0.52, 0.61)
	1.0	0.50 (0.47, 0.53)	0.86 (0.83, 0.89)	0.37 (0.34, 0.41)
	2.0	0.51 (0.47, 0.55)	0.88 (0.85, 0.92)	0.34 (0.30, 0.38)
	3.0	0.51 (0.46, 0.55)	0.84 (0.80, 0.89)	0.39 (0.33, 0.44)
LBD	0.5	0.22 (0.13, 0.33)	0.40 (0.24, 0.57)	0.96 (0.95, 0.97)
	1.0	0.18 (0.10, 0.28)	0.47 (0.29, 0.64)	0.96 (0.95, 0.97)
	2.0	0.18 (0.07, 0.30)	0.62 (0.33, 0.88)	0.96 (0.94, 0.97)
	3.0	0.20 (0.09, 0.33)	0.90 (0.57, 1.00)	0.95 (0.94, 0.97)
AD+LBD	0.5	0.38 (0.20, 0.58)	0.03 (0.01, 0.05)	0.98 (0.98, 0.99)
	1.0	0.44 (0.31, 0.57)	0.06 (0.04, 0.08)	0.96 (0.95, 0.97)
	2.0	0.54 (0.37, 0.70)	0.06 (0.04, 0.09)	0.97 (0.95, 0.98)
	3.0	0.39 (0.19, 0.58)	0.05 (0.02, 0.08)	0.96 (0.94, 0.98)
Neither	0.5	0.44 (0.40, 0.49)	0.65 (0.60, 0.69)	0.65 (0.62, 0.68)
	1.0	0.65 (0.59, 0.71)	0.54 (0.49, 0.59)	0.92 (0.90, 0.94)
	2.0	0.66 (0.57, 0.75)	0.53 (0.46, 0.62)	0.94 (0.92, 0.96)
	3.0	0.69 (0.60, 0.77)	0.63 (0.54, 0.71)	0.93 (0.90, 0.95)

Results

Figure 1: Significant results for clinical diagnostic disparities evaluated by false negative rate (FNR), precision (PPV), sensitivity and specificity for sex and race.



- Clinical AD+LBD diagnosis had poor sensitivity from 3% (CDR 0.5) to 6% (CDR 2.0) (Table 1). Over 60% of participants with autopsy-confirmed AD+LBD were diagnosed clinically as AD.
- Clinical AD diagnosis had low sensitivities at early dementia stage (57%) and low specificities at all stages. Among participants clinically diagnosed as AD, over 33% had autopsy-confirmed concurrent LBD neuropathology (Table 2).
- Clinical LBD diagnosis had poor PPV from mild cognitive impairment (22%) to severe dementia (20%). Within participants clinically diagnosed as LBD, 32% to 54% revealed autopsy-confirmed AD+LBD pathology.
- With increasing dementia stages, the difference in clinical diagnosis accuracy significantly increased between White and Black/African-American participants, and the diagnosis quality significantly improved for males but not for females (Figure 1).

Conclusion and Next Steps

- Dementia subtypes diagnosis in the clinic has low accuracy and biases against minor groups at all dementia stages, which will lower the quality of corresponding clinical trials
- Improving the diagnostic instruments, and developing more accurate imaging and cerebrospinal fluid biomarkers particularly for minority populations will be important steps towards better screening, diagnosis, and treatment design for dementia.