Validation of a Pre-Diagnostic Progression Rate Used to Predict Post-Diagnostic Change on Common Alzheimer's Disease Outcome Measures

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Background

- Individuals with Alzheimer's disease (AD) progress at different rates
- Estimating the intrinsic progression rate at time of initial workup can be useful for suggesting the underlying neuropathology and for patient and caregiver counseling
- Doody et al.[1] proposed that the rate of decline can be estimated at diagnosis, using Mini-mental State Exam score as a metric, by the formula:
  - (30 – current MMSE) / Duration of symptoms
    - Duration of symptoms must be carefully estimated by clinician during initial exam
- Since the initial MMSE and duration of symptoms are unobserved, a validation of this approach would support the use of this formula for calculating expected progression rate.

Aim

- To validate an estimated rate of cognitive decline calculated at time of AD diagnosis

Methods

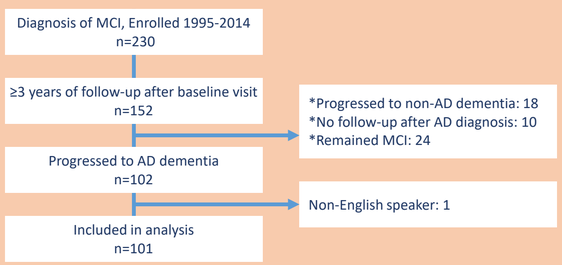
Setting:

- Academic Alzheimer's Center established in 1989
- Patients enrolled in a research database consisting of annual clinical evaluation and neuropsychological data
- Diagnosis by consensus conference following NINCDS-ADRDA criteria for AD, Petersen criteria for MCI

Patients:

- Patient enrolled between 1995 and 2014, initially diagnosed with MCI and progressed to AD dementia (Figure 1)

Figure 1. Subject Selection



Calculation of Pre-Progression Rate (PPR):

PPR = Annual decline on MMSE from first symptoms to diagnosis of AD

Observed PPR = (Baseline MMSE − MMSE at AD diagnosis) / years since MCI diagnosis

Estimated PPR = (30 – MMSE at AD diagnosis) / (Physician estimate of symptom duration + time from baseline to diagnosis of AD)

PPR dichotomized: "fast" (>2 points decline per year)
"slow" (≤2 points per year)

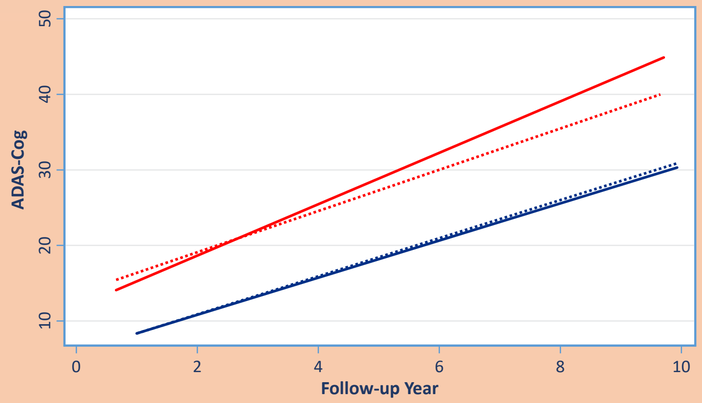
Analysis:

- Agreement between actual and estimated PPR assessed with the Kappa statistic
- Mixed effects regression models constructed to compare prediction of post-diagnosis progression using actual vs. estimated PPR
- Outcome measures were the MMSE, ADAS-Cog, CDR-SB

Table 1. Baseline Characteristics by Observed Pre-progression Group

	Slow (n=84)	Intermediate/Fast (n=17)	Total (n=101)	*p*-value
Age (years)	71.57 (6.63)	72.14 (7.34)	71.66 (6.72)	0.75
Sex (% female)	39 (46.43)	13 (76.47)	52 (51.49)	0.34
Years of Education	15.88 (3.23)	16.53 (3.68)	15.99 (3.30)	0.46
Race (% White)	80 (95.24)	15 (88.24)	95 (94.06)	0.32
MCI Subtype (%)				0.77
• Amnestic MCI	60 (71.43)	13 (76.47)	73 (72.28)	
• Non-Amnestic MCI	24 (28.57)	4 (23.53)	28 (27.72)	
APOE Genotype (% e4 positive) n=97	47 (58.02)	11 (68.75)	58 (59.79)	0.43
Baseline MMSE	27.38 (2.19)	26.76 (2.77)	27.28 (2.29)	0.31
ADAS-Cog n=98	9.57 (3.44)	12.04 (5.68)	9.97 (3.96)	0.11
CDR SB n=98	1.93 (1.56)	2.00 (1.57)	1.86 (1.55)	0.69
Years from Baseline to AD Conversion	3.07 (2.20)	1.32 (0.47)	2.78 (2.11)	<0.0001
Years of Follow-up After AD Conversion	3.71 (2.73)	3.61 (1.73)	3.69 (2.58)	0.85

Figure 3. Predicted ADAS-Cog Change Based on Observed vs. Predicted PPR



Results

- 101 subjects met inclusion criteria (Figure 1)
- 17 (17%) fast progressors, 84 (83%) slow progressors
- Fast and slow progressors differed only in time to conversion to AD (Table 1)
- 92% concordance between observed and estimated PPR (kappa=0.703)
- In mixed effects repeated regression models using first the actual PPR, then estimated PPR…
  - MMSE, ADAS-Cog and CDR-SB change after AD diagnosis had similar slopes
  - Small differences in slope for fast progressors likely due to small sample size
  - Both actual and estimated PPR predicted an acceleration of decline on the CDR-SB between slow and fast progressors

Figure 2. Predicted MMSE Change Based on Observed vs. Estimated PPR

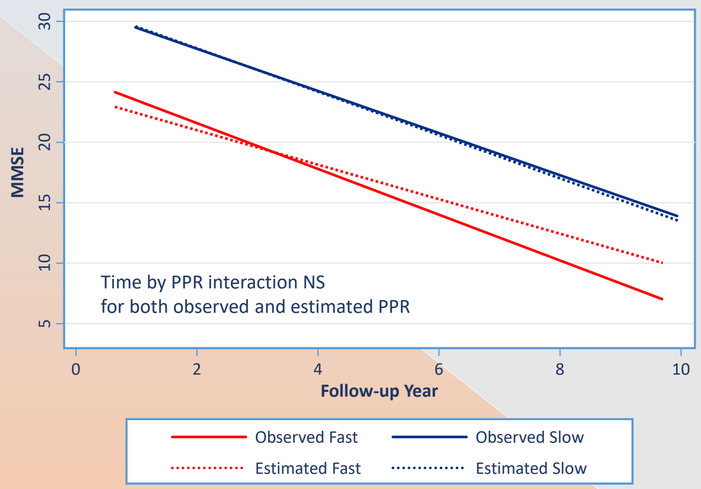
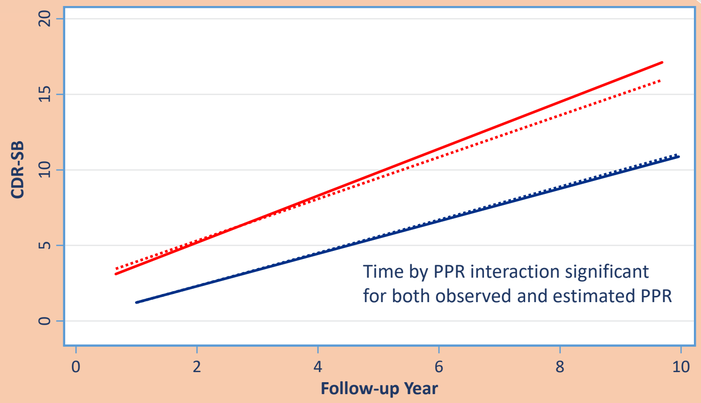


Figure 4. Predicted CDR-SB Change Based on Observed vs. Fast PPR



Conclusions

- The estimated PPR, based on an assumed initial MMSE score of 30 and a careful estimate of symptom duration, appears valid, and is a convenient tool for management and family counseling.
  - Accuracy depends on careful estimate of duration of symptoms using methods proposed by Doody et al.[2]

Limitations

- Fast progressors represented a small fraction of the total sample, and thus, model estimates for this group may be unstable.
- The MMSE is only one possible metric to define progression rate.

References

1. Doody RS, Massman P, Dunn JK. A method for estimating progression rates in Alzheimer disease. Arch Neurol. 2001; 58(3):449-54.
2. Doody RS, Dunn JK, Huang E, Azher S, Kataki M. A method for estimating duration of illness in Alzheimer's disease. Dement Geriatr Cogn Disord. 2004;17(1-2):1-4.

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