



Cognitive function and neuropathological outcomes: a forward-looking approach

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Abstract

Objective To evaluate the risk of Alzheimer’s disease-related neuropathology burden at autopsy given older adults’ current cognitive state.

Method Participants included 1,303 individuals who enrolled in the Religious Orders Study (ROS) and 1,789 who enrolled in the Rush Memory and Aging Project (MAP). Cognitive status was evaluated via standardized assessments of global cognition and episodic memory. At the time of analyses, about 50% of participants were deceased with the remaining numbers right censored. Using multi-state Cox proportional hazard models, we compared the cognitive status of all subjects alive at a given age and estimated future risk of dying with different AD-related neuropathologies. Endpoints considered were Braak Stages (0–2, 3–4, 5–6), CERAD (0, 1, 2, 3), and TDP-43 (0, 1, 2, 3) level.

Results For all three pathological groupings (Braak, CERAD, TDP-43), we found that a cognitive test score one standard deviation below average put individuals at up to three times the risk for being diagnosed with late stage AD at autopsy according to pathological designations. The effect remained significant after adjusting for sex, APOE-e4 status, smoking status, education level, and vascular health scores.

Conclusion Applying multi-state modeling techniques, we were able to identify those at risk of exhibiting specific levels of neuropathology based on current cognitive test performance. This approach presents new and approachable possibilities in clinical settings for diagnosis and treatment development programs.

Keywords Alzheimer’s disease · Neuropathology · Cognition · Multi-state model

Introduction

Understanding how the underlying pathology of individuals with possible or probable Alzheimer’s disease (AD) affects current cognitive states as well as future cognitive outcomes remains an open area of research. Utilizing post-mortem

data, greater levels of pathology assessed at autopsy tend to be associated with lower antemortem average cognitive function and steeper terminal cognitive decline, regardless of whether the patient had been diagnosed with AD or not [1–6]. Of great empirical and clinical interest, however, is to understand how underlying brain pathology may be

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affecting cognitive function and decline in living individuals to increase diagnostic precision [7] and develop effective treatment plans.

Multiple landmark aging studies have gathered rich measures of brain pathology but due to the nature of the assessment procedures, such data can only be obtained when participants have undergone autopsy. This implies that any inference about the forward relationship of pathology on cognition must be indirect, being based on a reversal of temporal ordering. A method commonly used, for example, is to categorize individuals by their final pathology and then ‘look backwards’ at each individual’s average cognitive function and cognitive trajectories. A modeling approach would then be to treat cognition as an outcome, with age and pathology as predictors, despite the pathology variables being collected after cognition. An assumption implicit in this approach is that pathology observed at autopsy was operative earlier in each individual’s life; while this is likely a reasonable assumption, it may not necessarily be the case and becomes less likely at longer intervals between cognitive testing and death. In the present study, we avoid the reversal of temporal ordering by implementing a multi-state modeling approach to predict the likelihood that a certain neuropathological outcome will result based on a given individual’s current cognitive function profile during study participation.

To our knowledge, studies are yet to examine how cognitive function profiles may put a person at risk of exhibiting a specific pathology at autopsy. Using a multi-state modeling technique, we can examine how an individual’s current cognitive state predicts the risk of AD-related neuropathology found post-mortem. This ‘forward looking’ approach has some key advantages. First, this approach utilizes information from all available subjects, both living and deceased, compared to a ‘looking back’ approach that only uses data from deceased and autopsied individuals. Second, and most important, results from this analysis may ultimately be useful for individual patient prediction in clinical settings, implementation of relevant preventative treatments, and for long-term treatment planning. Such an approach, thus, allows a forward prediction line of reasoning that more closely matches theoretical accounts [8] and can be clinically informative.

Method

Participants

Participants were part of two large longitudinal clinical-pathologic cohort studies of dementia, the Religious Orders Study (ROS) and the Rush Memory and Aging Project (MAP) [9, 10]. ROS participants are older Catholic nuns, priests, and brothers who agreed to participate in annual

clinical evaluations and brain donation at death. This study was approved by the Institutional Review Board of Rush—Presbyterian—St. Luke’s Medical Center. The ROS sample consisted of 1,303 individuals, 70.83% of whom were female and were 75.92 years old at baseline ($SD = 7.44$, range = 55–103). ROS incorporated cognitive assessments for up to 20 years. MAP consists of older community-dwelling adults who agreed to participate in annual clinical evaluations and brain donations at death. The study was approved by the Institutional Review Board of Rush University Medical Center. MAP participants consisted of 1,789 individuals, 73.39% of whom were female and were 79.94 years old on average at baseline ($SD = 7.64$, range = 53–101). The MAP study incorporated annual cognitive assessments for up to 17 years.

The total sample for our current analysis consisted of 3,092 individuals with an average of 6.8 years of annual assessments ($SD = 5.4$, range = 0–22). At the time of data analysis, roughly 50 % ($N = 1492$) of participants were deceased; mean age at death was 88.4 years ($SD = 6.6$, range = 65–108). The average time between the last cognitive assessment and death was 0.90 years ($SD = 1.23$). We did not exclude participants with other neurodegenerative disorders, such as Lewy Body dementia, because we were interested in assessing the prediction of AD neuropathologies irrespective of the classification of the underlying disease. Table 1 presents additional descriptive data. Data distribution for the current analyses was approved by the committee of the Rush Alzheimer’s Disease Research Center.

Table 1 Descriptive summary of all participants

	Total	MAP	ROS
<i>N</i>	3092	1789	1303
Baseline % MCI/dementia	25.2/6.1	26.0/5.4	24.1/7.1
Age	78.25 (7.8)	79.94 (7.6)	75.92 (7.4)
Female (%)	2236 (72.32)	1313 (73.39)	923 (70.84)
APOe4 (%)	690 (22.32)	386 (21.58)	304 (23.33)
Smoker (%)	1065 (34.44)	797 (44.55)	268 (20.57)
Global cognition	0.02 (0.70)	− 0.03 (0.7)	0.09 (0.6)
Episodic memory	0.01 (0.81)	− 0.08 (0.84)	0.13 (0.73)
Vascular score	0.94 (0.80)	1.08 (0.8)	0.76 (0.7)
Years of Education	16.12 (3.8)	14.56 (3.3)	18.26 (3.3)
< HS (%)	186 (6.02)	155 (8.66)	31 (2.38)
HS (%)	970 (31.37)	853 (47.68)	117 (8.98)
College (%)	1607 (51.97)	720 (40.25)	887 (68.07)
Graduate school (%)	329 (10.64)	61 (3.41)	268 (20.57)

Continuous variables are expressed as mean (SD), factors are expressed as counts (%)

HS high school

Pathologic outcome categories

We examined three types of pathological endpoints that are associated with AD pathology; Braak staging, Consortium to Establish a Registry for Alzheimer's disease (CERAD) protocol [11] scoring, and a Transactive Response DNA Binding Protein (TDP-43) Score. Recently, TDP-43 has gained traction as a post-mortem marker of AD, through both β -amyloid dependent and β -amyloid independent pathways [12, 13]. Neurofibrillary tangles (NFTs) and neuritic plaques were visualized using Bielschowsky silver stain [14] and immunohistochemistry was used for TDP-43 using a rat phosphorylated monoclonal TAR5P-1D3 TDP-43 antibody (see Nag et al., 2015 for details) [15, 16].

Braak stages

Briefly, Braak and Braak described a staging scheme of NFTs [17], which proposes six stages that can be reduced to four with improved inter-rater reliability [18]: (1) No NFTs; (2) Braak stages I/II—NFTs predominantly in entorhinal cortex and closely related areas; (3) Braak stages III/IV—NFTs more abundant in hippocampus and amygdala while extending slightly into association cortex; and 4) Braak stages V/VI with NFTs widely distributed throughout the neocortex and ultimately involving primary motor and sensory areas. This staging scheme covers early lesions in the entorhinal cortex to the primary neocortex [19]. For our purposes, we combined the first two of these stages, as both No NFTs and Braak stages I/II represent little to no AD pathology resulting in three stage categories: (1) 0–2, (2) 3–4, and (3) 5–6.

CERAD

The CERAD scoring is a semi-quantitative measure of the neuritic plaques in the brain. The CERAD score we used converts the standard CERAD score to indicate the extent of AD diagnostic certainty post-mortem [19, 20], with a score of 0 indicating no AD, 1 indicating possible AD, 2 indicating probable AD, and 3 indicating definite likelihood of AD [11]. Like the NFTs scoring, this score was averaged across six brain regions from the entorhinal cortex to the primary neocortex; indices across each specific brain region were strongly correlated and were, thus, averaged to create one composite score to reduce measurement error (see Wilson et al., 2007 for additional details) [19].

TDP-43

The final endpoint we considered was the TDP-43 score with a score of 0 representing no TDP-43 pathology, and Stage 1, Stage 2, and Stage 3 representing increasing levels

of TDP-43 pathology in amygdala, hippocampus and/or entorhinal cortex, and the neocortex, respectively [21].

Cognitive performance assessments

The present analysis employs measures of global cognition and episodic memory; we elected to focus on these two cognitive indices given that memory concerns and global functioning are the most typically assessed cognitive domains in clinical settings. Moreover, episodic memory difficulties have been closely linked with the early stages of AD pathogenesis. Participants in the ROS and MAP studies underwent annual cognitive testing and were administered 19 common cognitive performance tests, as described in detail in the previous publications [9, 22]. In brief, the 19 cognitive tests included measures of episodic memory, language function, working memory, processing speed, and visuospatial ability. For the global cognition indicator, scores from the 19 tests were converted to Z-scores using the baseline mean and standard deviations from the full cohort and averaged to form a measure of global cognition [23, 24]. The composite Episodic Memory Score was based on scores from immediate and delayed recall performance from Logical Memory, the East Boston Story, Word List Memory Recall, and Recognition from the CERAD. Raw scores on each of the tests were Z-scored, using the baseline mean and standard deviation from the full cohort, and averaged to yield a composite Episodic Memory Score.

Statistical analyses

A multi-state model can be viewed as an extension of the standard survival curve analysis that only has two end states (i.e., alive and dead; panel A in Fig. 1) but where multiple end states can be estimated, such as CERAD states 0, 1, 2, or 3 or alive (i.e., five end states). The parameters of interest are the transition rates to different states (e.g., to CERAD 0 or CERAD 1; see panel B in Fig. 1). This model allows for each risk rate to vary by age, and thus the estimated transition rates correspond to a specific age.

We fit a series of six multi-state models, one for each pathologic outcome category (Braak, CERAD, and TDP score), separately for Global and Episodic Memory Scores to determine how each cognitive score influenced the risk of specific neuropathological outcome states. Aside from cognitive status, the only time varying covariate was vascular risk score. Age was used as the time scale and the analysis was stratified on study (ROS/MAP), thus hazard ratios compare a subject with given covariates to others of the same age and study population.

Demographic and health variables controlled for in the adjusted models were: sex, education level, APO-e4 status, vascular risk, and smoking status. Vascular risk was a

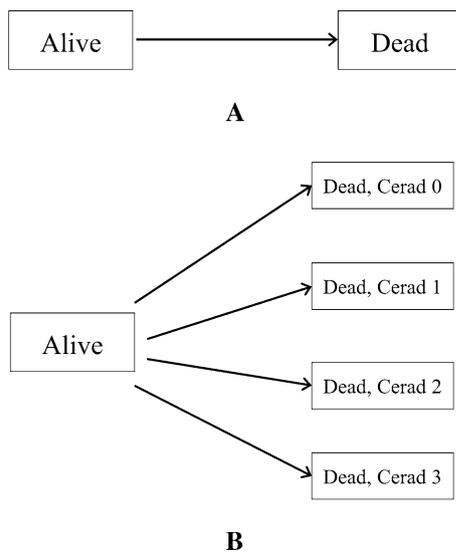


Fig. 1 **a** Exemplar diagram of a two-state survival model; **b** exemplar diagram of a multi-state model for CERAD end states. Similar models were fit for Braak and TDP-43 states. Models allowed each risk to vary by age so that estimated risks correspond to a specific age

composite score that assessed burden based on hypertension, diabetes, and smoking history. In addition, we controlled for follow-up year. For each pathological outcome category, an individual was considered censored if they were still alive at the end of the study time frame. All analyses were performed using R version 3.1.2 [25] and the ‘survival’ package [26, 27].

Results

Descriptive summaries of the study sample report continuous variables as mean and standard deviation; frequencies and percentages are presented for the categorical variables (see Table 1). Descriptive summaries of autopsied participants are presented in Table 2. At autopsy, 228 (15%) persons had no evidence of neurofibrillary tangles according to Braak staging procedures, and 310 (22%) had evidence of the most severe pathology. Two-hundred and ninety-six (19%) persons had no AD according to CERAD scoring, and 402 (27%) were classified as definite AD. Five-hundred and twenty-two persons (35%) had no TDP-43 pathology and 140 (9.4%) were classified in the third stage of TDP-43. Table 2 shows cognition scores and a demographic breakdown for each of the endpoints.

Multi-State model results

The primary analysis consisted of fitting three separate multi-state models; one for each of the pathological outcome categories (i.e., Braak, CERAD, and TDP-43). We used Aalen–Johansen estimators [28] within each pathological outcome category to estimate time-to-outcome curves for each pathological outcome endpoint, as well as for the total group. Table 3 contains the simple and adjusted Cox model fit parameters for all endpoints representing the hazard ratio along with the 95% confidence interval for the covariates of interest: global cognition or episodic memory. Because the scores we used in the current analysis were standardized

Table 2 Descriptive summary of autopsied participants’ pathology indices, cognitive scores, and demographic covariates

End stage	N	Age	Female (%)	APOe4 (%)	Smoker (%)	Global cognition	Episodic	Vascular score	Education
<i>Braak</i>									
0–2	228	77.3 (7.2)	116 (50.88)	39 (17)	77 (34)	– 0.32 (1)	– 0.13 (1.2)	1.16 (0.8)	16.91 (3.8)
3–4	715	81.67 (6.9)	469 (65.59)	151 (21)	205 (29)	– 0.74 (1)	– 0.70 (1.2)	1.01 (0.9)	16.25 (3.6)
5–6	310	81.44 (5.7)	229 (73.87)	139 (45)	88 (28)	– 1.89 (1.2)	– 2.03 (1.2)	1.03 (0.8)	16.1 (3.6)
Braak missing	239	81.1 (6.7)	161 (67.36)	54 (22)	89 (37)	– 0.86 (1)	– 0.82 (1.2)	1.25 (0.9)	15.04 (4)
<i>CERAD</i>									
0	296	79.09 (7.5)	175 (59.12)	28 (10)	94 (32)	– 0.36 (1)	– 0.21 (1.1)	1.1 (0.9)	16.44 (3.8)
1	124	80.72 (6.8)	73 (58.87)	22 (18)	31 (25)	– 0.49 (0.9)	– 0.38 (1.1)	1.05 (0.8)	16.47 (3.5)
2	431	81.79 (7)	268 (62.18)	105 (24)	130 (30)	– 0.93 (1.1)	– 0.92 (1.3)	1.03 (0.9)	16.29 (3.7)
3	402	81.08 (6.2)	298 (74.13)	174 (43)	115 (29)	– 1.54 (1.3)	– 1.62 (1.4)	1.02 (0.8)	16.25 (3.6)
CERAD missing	239	81.1 (6.7)	161 (67.36)	54 (23)	89 (37)	– 0.86 (1)	– 0.82 (1.2)	1.25 (0.9)	15.04 (4)
<i>TDP-43</i>									
0	522	79.51 (7.1)	331 (63.41)	107 (21)	158 (30)	– 0.72 (1.1)	– 0.61 (1.3)	1.08 (0.9)	16.16 (3.8)
1	166	81.45 (6.9)	115 (69.28)	35 (21)	49 (30)	– 0.72 (1.1)	– 0.61 (1.2)	1.15 (0.9)	15.76 (3)
2	203	81.76 (6.5)	148 (72.91)	66 (33)	65 (32)	– 1.27 (1.2)	– 1.32 (1.4)	1.07 (0.9)	16.15 (3.5)
3	140	82.05 (6.5)	95 (67.86)	52 (37)	39 (28)	– 1.71 (1.2)	– 1.93 (1.4)	1.03 (0.8)	15.84 (3.5)
TDP missing	461	81.43 (6.6)	286 (62.04)	123 (27)	148 (32)	– 0.87 (1.1)	– 0.85 (1.3)	1.06 (0.9)	16.29 (4.1)

Table 3 Hazard ratios and 95% confidence interval (CI) for a one-unit lower cognitive score

	Global unadjusted (95% CI)	Episodic unadjusted (95% CI)	Global adjusted (95% CI)	Episodic adjusted (95% CI)
Braak 0–2	1.30 (1.12, 1.47)	1.09 (0.96, 1.22)	1.33 (1.15, 1.51)	1.11 (0.97, 1.25)
Braak 3–4	1.47 (1.37, 1.57)	1.32 (1.24, 1.39)	1.51 (1.41, 1.62)	1.34 (1.26, 1.43)
Braak 5–6	2.96 (2.7, 3.21)	2.77 (2.53, 3.02)	2.99 (2.73, 3.25)	2.79 (2.54, 3.04)
Cerad 0	1.21 (1.07, 1.36)	1.06 (0.95, 1.17)	1.24 (1.09, 1.39)	1.07 (0.96, 1.19)
Cerad 1	1.22 (1.00, 1.44)	1.1 (0.93, 1.27)	1.25 (1.02, 1.48)	1.11 (0.93, 1.29)
Cerad 2	1.67 (1.53, 1.81)	1.49 (1.38, 1.60)	1.72 (1.57, 1.86)	1.52 (1.4, 1.63)
Cerad 3	2.48 (2.31, 2.68)	2.25 (2.09, 2.42)	2.55 (2.35, 2.74)	2.29 (2.12, 2.46)
TDP 0	1.56 (1.43, 1.68)	1.33 (1.24, 1.43)	1.58 (1.46, 1.71)	1.35 (1.25, 1.45)
TDP 1	1.44 (1.24, 1.65)	1.22 (1.07, 1.38)	1.48 (1.27, 1.7)	1.25 (1.09, 1.41)
TDP 2	2.01 (1.78, 2.24)	1.79 (1.6, 1.98)	2.07 (1.84, 2.31)	1.83 (1.64, 2.03)
TDP 3	2.66 (2.31, 3.01)	2.59 (2.24, 2.94)	2.72 (2.36, 3.08)	2.64 (2.29, 3.00)
Overall	1.78 (1.26, 2.29)	1.56 (1.12, 1.99)	1.81 (1.27, 2.36)	1.58 (1.13, 2.03)

All models are stratified by study, the adjusted models contain sex, apoe4, smoking, education, vascular score, and follow-up year as covariates

to have a mean of zero and a standard deviation of one, a one-point decrease in the cognitive scores is equivalent to a one standard deviation (SD) decrease from the mean. A follow-up analysis consisted of fitting an additional multi-state model for all possible Braak/CERAD pathology combinations; we did not include mixed pathology combinations with TDP-43 due to the low frequencies of combinations given that TDP-43 measurements were introduced later in the studies. The simple and adjusted hazard ratios in Table 4 represent the risk of having a given co-pathology at autopsy.

Results by endpoint

Braak

Table 3 can be interpreted in the following manner. An individual with a current score one point (i.e., one SD)

lower than the average global cognition score has an increased risk of Braak 0–2 death by 1.30-fold, compared to someone who is the same age and sex and with an average cognitive score. Equivalently, a current score one point higher in global cognition decreases the risk of Braak 0–2 death by 1.30-fold. The risk of a Braak 3–4 death increases by 1.47 for a current global cognition score that is one point lower than the average, but this is not statistically different than that for Braak 0–2 death. Alternatively, an individual with a current global cognition score that is one point lower than average has a significant almost threefold (2.96; $p < 0.05$) increased risk of a Braak 5–6 death compared to a Braak 0–2 death. A graphical exemplar of these results is presented in Fig. 2, which shows the absolute risk curves for Braak stages 0–2, 3–4, and 5–6 at age 70 for someone with an average global cognitive score (0) compared to scores one standard deviation above (+1)

Table 4 Co-pathology hazard ratios for a one-unit lower cognitive score

	N	Global unadjusted (95% CI)	Episodic unadjusted (95% CI)	Global adjusted (95% CI)	Episodic adjusted (95% CI)
Braak 0–2/Cerad 0	123	1.16 (0.93, 1.39)	0.96 (0.79, 1.14)	1.18 (0.95, 1.42)	0.98 (0.8, 1.16)
Braak 0–2/Cerad 1	39	1.19 (0.79, 1.59)	0.96 (0.66, 1.25)	1.23 (0.82, 1.65)	0.98 (0.68, 1.28)
Braak 0–2/Cerad 2	47	1.43 (1.02, 1.83)	1.21 (0.9, 1.51)	1.48 (1.06, 1.89)	1.24 (0.92, 1.55)
Braak 0–2/Cerad 3	19	2.00 (1.27, 2.74)	1.88 (1.23, 2.52)	2.04 (1.3, 2.77)	1.9 (1.25, 2.54)
Braak 3–4/Cerad 0	173	1.25 (1.06, 1.44)	1.12 (0.97, 1.26)	1.27 (1.08, 1.47)	1.13 (0.98, 1.28)
Braak 3–4/Cerad 1	84	1.24 (0.98, 1.5)	1.16 (0.95, 1.37)	1.26 (0.99, 1.54)	1.17 (0.95, 1.38)
Braak 3–4/Cerad 2	300	1.51 (1.35, 1.66)	1.37 (1.24, 1.49)	1.57 (1.41, 1.73)	1.4 (1.27, 1.53)
Braak 3–4/Cerad 3	158	1.75 (1.51, 1.98)	1.53 (1.34, 1.72)	1.8 (1.56, 2.04)	1.57 (1.38, 1.76)
Braak 5–6/Cerad 1	1	0.98 (– 1.22, 3.19)	1.07 (– 0.83, 2.98)	1.02 (– 1.21, 3.26)	1.11 (– 0.79, 3.01)
Braak 5–6/Cerad 2	84	2.45 (2.04, 2.87)	2.2 (1.83, 2.57)	2.43 (2.02, 2.85)	2.19 (1.82, 2.55)
Braak 5–6/Cerad 3	225	3.17 (2.86, 3.49)	3.05 (2.72, 3.37)	3.23 (2.9, 3.56)	3.08 (2.75, 3.41)

All models are stratified by study, the adjusted models contain sex, apoe4, smoking, education, vascular score, and follow-up year as covariates

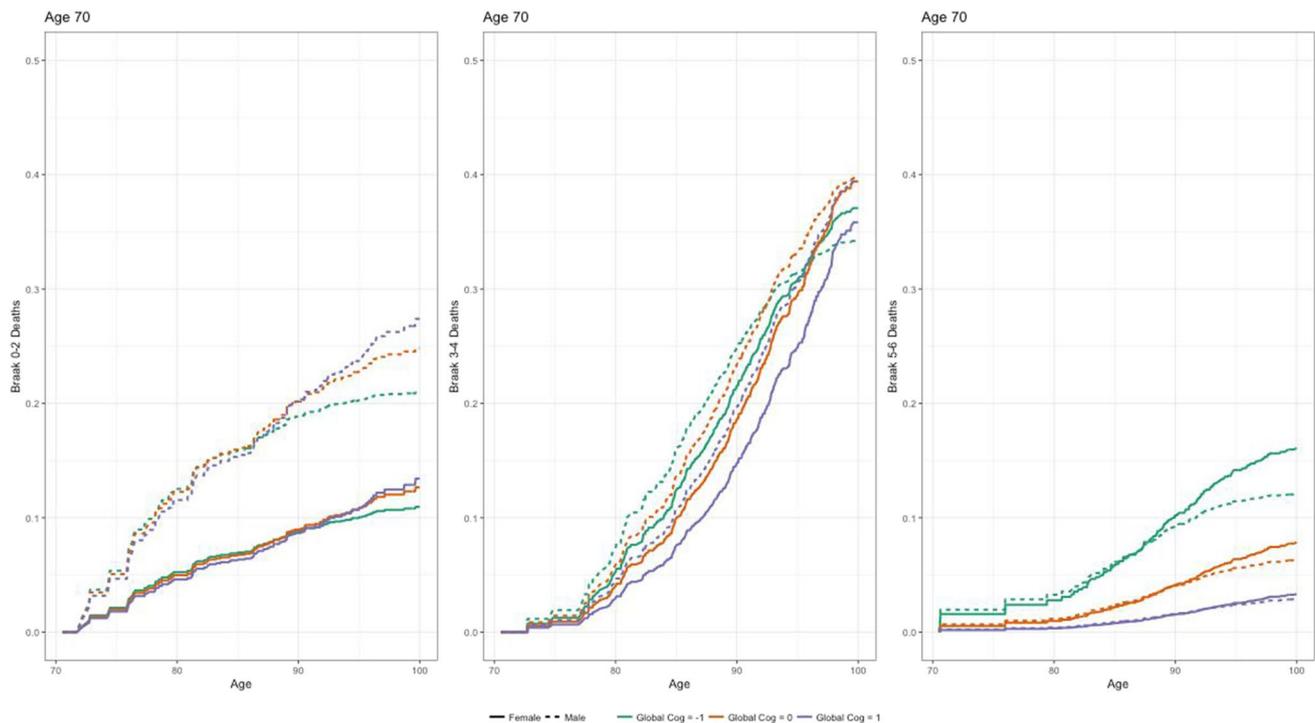


Fig. 2 Absolute risk curves for Braak stages 0–2, 3–4, and 5–6 among college-educated female/male at age 70

or below average (-1). Similar plots can be generated at any age.

Results for episodic memory indicate that a one point lower score in this domain increases the risk 1.09-fold of a Braak 0–2 death, by 1.32-fold for that of a Braak 3–4 death, and 2.77-fold for that of a Braak 5–6 death; these differences were all statistically significant ($p < 0.01$).

CERAD

Each one point lower score in global cognition does not significantly increase the risk of CERAD 0 (no AD) or of CERAD 1 (possible AD), as indicated by confidence intervals that include 1. A one point lower score in global cognition does significantly increase the risk of both a CERAD 2 and CERAD 3 death by 1.67- and 2.48-fold, respectively. This finding was similar for Episodic Memory Scores. The added risks of a CERAD 0 and 1 death from a one point decrease in episodic memory were not statistically significant, but were statistically significant for a CERAD 2 and 3 deaths (1.49 and 2.25, respectively).

TDP-43

Each one point lower score in global cognition significantly increases the risk of death with a TDP-43 0 or 1 by 1.55- and 1.44-fold, respectively; the risk for TDP-43 0 was not

statistically different than that for TDP-43 1. Further, the added risk of a one point decrease in global cognition significantly increases to 2.01 and 2.48 for a TDP-43 2 and 3 deaths, respectively. A similar pattern is found for Episodic Memory Score.

An examination of the hazard ratios for the adjusted versus unadjusted model results shows that the effect of both global cognition and episodic memory on the endpoints changes little when adjusted for other variables.

Co-pathology endpoints

Results for the co-pathology combinations confirmed the results described above and are presented in Table 4. A one-unit lower score in global cognition and episodic memory increased the risk of death with the more severe pathology combinations. One-unit lower score in both global cognition and episodic memory was related to more than a threefold increased risk of a Braak 5–6 and CERAD 3 combination. Comparatively, a one-unit lower score in global cognition was not likely to result in Braak 5–6/CERAD 1 death (0.98). Furthermore, a supplementary analysis of competing risks for death with autopsy versus death without autopsy (i.e., having a missing pathology score) is presented in Table 5; these results suggest that there is no autopsy bias in our results (i.e., individuals with greater pathology were not less likely to get autopsied).

Table 5 Hazard ratios and 95% confidence interval (CI) for death with autopsy versus death without autopsy

	Global unadjusted (95% CI)	Episodic unadjusted (95% CI)	Global adjusted (95% CI)	Episodic adjusted (95% CI)
Braak miss	1.78 (1.58, 1.97)	1.53 (1.37, 1.68)	1.77 (1.56, 1.99)	1.53 (1.36, 1.70)
Cerad miss	1.78 (1.58, 1.97)	1.53 (1.37, 1.68)	1.77 (1.56, 1.99)	1.53 (1.36, 1.70)
TDP miss	1.81 (1.67, 1.95)	1.61 (1.49, 1.72)	1.83 (1.68, 1.98)	1.63 (1.5, 1.75)
Braak/cerad Missing	1.78 (1.58, 1.97)	1.53 (1.37, 1.68)	1.77 (1.56, 1.99)	1.53 (1.36, 1.70)

All models are stratified by study, the adjusted models contain sex, apoe4, smoking, education, vascular score, and follow-up year as covariates

Discussion

We employed multi-state Cox proportional hazard models to determine the extent to which cognitive performance profiles at a given age increase the risk of exhibiting AD-related pathology, including amyloid plaques, neurofibrillary tangles, and TDP-43, at autopsy. We found that individuals who score one-point lower than their peers of the same age on composite scores of either global cognitive function or episodic memory may have up to a threefold risk of exhibiting severe AD-related pathology at autopsy.

To our knowledge, no studies have evaluated the future risk of having AD-related pathology, as indexed by CERAD, Braak staging, and TDP-43, based on a cognitive score. Multiple studies have shown that individuals who eventually receive an AD diagnosis or have AD-related pathology at autopsy performed more poorly on cognitive tests at baseline [29–31] and show steeper declines in performance longitudinally [2, 6]. However, these studies employ modeling techniques that incorporate a reverse causality such that analyses are conducted after an AD diagnosis is already made or autopsies have been conducted. Although some may argue that having more data on previous cognitive visits is beneficial because it improves precision of change parameters, this also stretches the assumption that pathology is constant throughout the study period.

We do not make that assumption in this study and instead make use of all available repeated assessment data from ROS and MAP to derive predictions based on individuals who have undergone autopsy and those who remain in the study. One previous study incorporated a similar approach by investigating the risk of dementia diagnosis based on baseline and longitudinal change in cognitive scores using a joint survival and growth models [32]. The authors found that lower baseline level of episodic memory was associated with AD onset risk [32]. In extension of that finding, we demonstrate that individuals with lower current scores on measures of global cognition and episodic memory have elevated risks of more severe AD pathology at autopsy, as compared to their age-matched peers.

We observed parallel results between a composite of global cognition and episodic memory; we chose to

separately evaluate the effect of episodic memory given that this cognitive domain is affected earliest in AD pathogenesis [33]. The similar effects of global cognition and episodic memory suggest the potential viability of implementing either a focused assessment of memory or a comprehensive, multi-domain approach to predict AD pathology risk. Nonetheless, we cannot rule out the possibility that other specific tasks will have equal or even greater predictive power given that we did not evaluate non-memory measures on an individual domain basis. For example, some studies have shown that tasks of executive function may also be predictive of AD [34]. Future studies testing similar or differential predictability of specific cognitive abilities will be informative for uncovering the cognitive measures that are most sensitive to detect the likelihood of specific pathologies at autopsy.

Results were parallel across Braak and CERAD, which are two traditional markers of AD, and with TDP-43. TDP-43 brain pathology is associated with more rapid cognitive decline and with lower baseline level of cognitive function compared to other neuropathologies of AD [35, 36]. This protein aggregate has been primarily implicated in fronto-temporal dementia, but some evidence indicates that it is also implicated in forming pathological aggregates in AD and thus may also be implicated in cognitive dysfunction in this disorder [35–37]. Further, TDP-43 is strongly correlated with tangles and these two pathologies may interact to exacerbate progression of cognitive decline. Future analytic efforts examining the predictive utility of cognitive status in the presence of mixed pathologies that include TDP-43 will be invaluable in determining the possible role of this marker on the rate of AD progression. This approach was not feasible in the current study due to the smaller sample size of those evaluated for TDP-43, but sample size is increasing with ongoing data collection.

Our results may have diagnostic and clinical trial implications. First, these findings suggest that lower performance on measures of memory or global cognitive functions may warrant additional clinical workup, or at the least suggest a potentially elevated risk profile for later AD pathology. Although this appears clinically intuitive, it is worth noting that our sample was comprised of 68% individuals who presented with no diagnosis of MCI or dementia and/or no clear

cognitive complaints at baseline; thus, it is possible that more routine screenings of cognitive status in aging adults may provide insights into who may be at greater risk for developing AD pathology, which in turn may inform early treatment plans. Given that AD clinical trials have begun to target earlier stages of clinical symptomatology, extending back even to asymptomatic stages, these risk factors and subtle cognitive warning signs may be even more prudent to assess. Further, given amyloid imaging techniques, which are highly predictive of AD but costly, monitoring of cognitive performance may serve as a complementary inexpensive strategy to identify those who may need to be imaged. In line with these considerations, results from our study may also be relevant to the identification and selection of candidate individuals for the development of trial ready cohorts. That is, clinicians would better know which subjects to refer for relevant trials, especially trials that would involve autopsies at their conclusion.

There are strengths and limitations to this study. The multi-state models we specified use cognition as a predictor of pathology but it is worth noting that these are not causative models as it is unlikely that lower cognitive status creates plaques or tangles. Instead, we can determine how these pathology markers may be operating prior to autopsy or clinical diagnosis. Future work incorporating AD biomarkers would be informative in validating the temporal ordering of factors leading up to AD diagnosis. A limitation of our study is that we did not examine effects on other pathology outcomes and we cannot be certain if a one unit lower score in global cognition or episodic memory is specific to AD pathology or just sensitive to it. Further, our pathology quantifications involved indices averaged across different brain regions and did not provide specificity on brain region accumulation or loss of synaptic function. Future studies evaluating region-specific neuropathological alterations would be informative. Last, findings from these analyses cannot be generalized more broadly to the population given the selectivity of the cohorts we analyzed, including their lack of ethnic and racial diversity [39].

Strengths of this study are in the use of multi-state proportional hazard models that make use of all available data and do not exclude any individuals who do not undergo autopsy or who are still alive, thus avoiding possible bias in our analytic sample. A key strength of employing this method is the ability to estimate the risk of a given neuropathological outcome without reversing the temporal ordering of this process. This model fitting approach also allowed us to evaluate whether there was an autopsy bias and results from Table 5 indicate that there is no autopsy bias, thus increasing the validity of these pathology results. One relevant future direction that would promote the clinical usability of the current findings would be to index the predictive power of the individual cognitive tests comprising

the composites used in this study. This would enable standardized approaches for determining the range of scores most associated with AD pathology risk.

In conclusion, this study demonstrated the utility of applying multi-state Cox proportional hazard models to predict neuropathological risk. We found that those with lower than average cognitive performance may have up to a threefold increased risk of more severe AD neuropathology at autopsy. With the advent of more involved imaging tests to predict pathological outcomes, this study demonstrates the utility of monitoring cognitive performance profiles that could be used complementarily with newer diagnostic tools.

Author contributions All authors developed the study concept. EM drafted the manuscript. TF performed the data analysis. TF and EM interpreted the results under the supervision of TT, BB, TH, DM, DT, TT, and DM provided comprehensive and critical revisions. All authors approved the final version of the manuscript submission.

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Compliance with ethical standards

Conflicts of interest The authors have no relevant conflict of interest to report.

Ethical standards The studies reported in this manuscript were approved by the Institutional Review Board of Rush—Presbyterian—St. Luke's Medical Center and the Institutional Review Board of Rush University Medical Center.

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