Factors Associated with Survival Probability in Autopsy-Proven Frontotemporal Lobar Degeneration

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CCEB

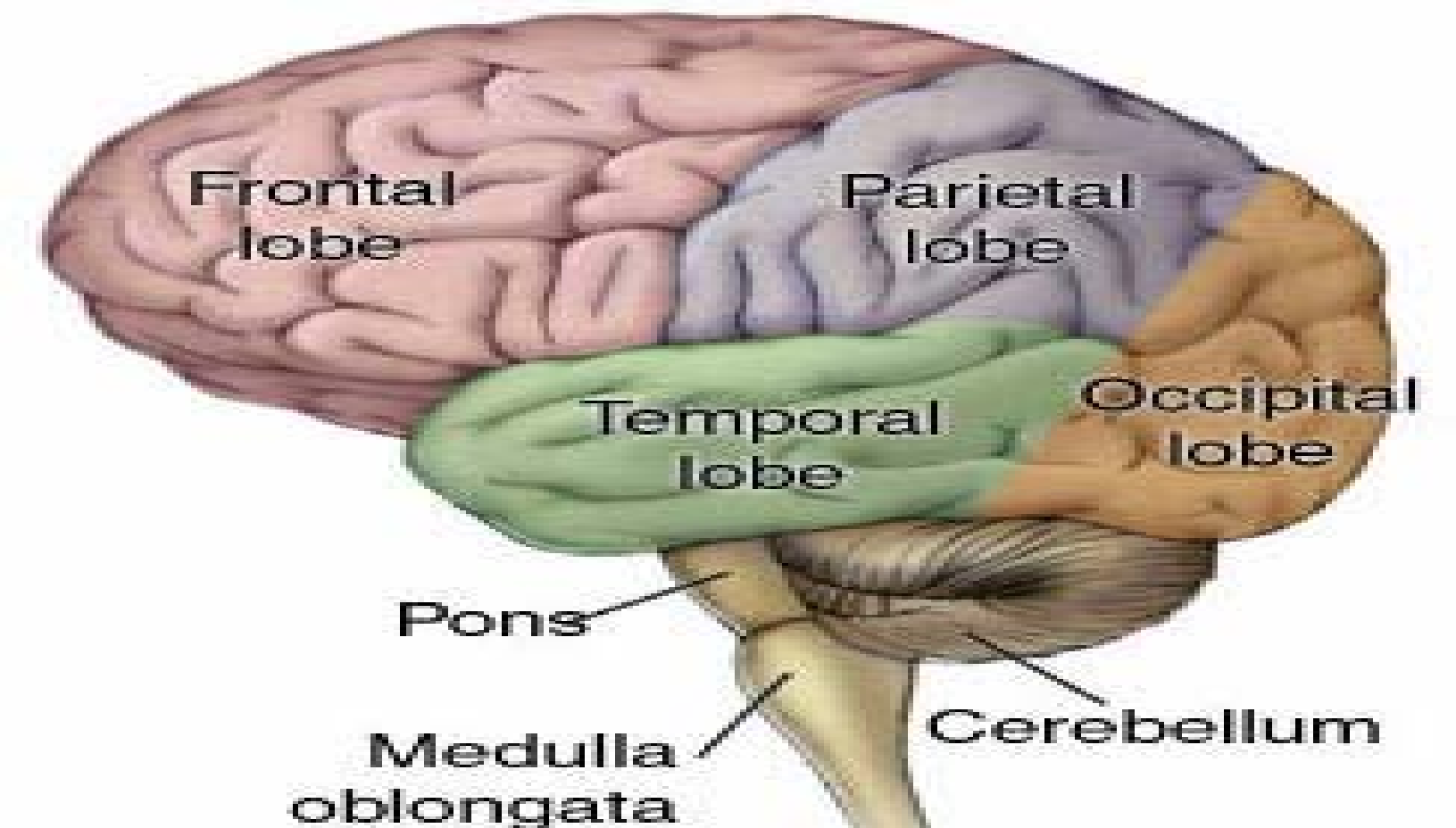
Background: Definition

Frontotemporal lobar degeneration (FTLD):

- Progressive neurodegenerative condition
- Progressive changes in behavior
- Progressive language dysfunction

Background: Brain Regions

- FTLD due to disease of frontal + temporal lobes:



Background: Pathology

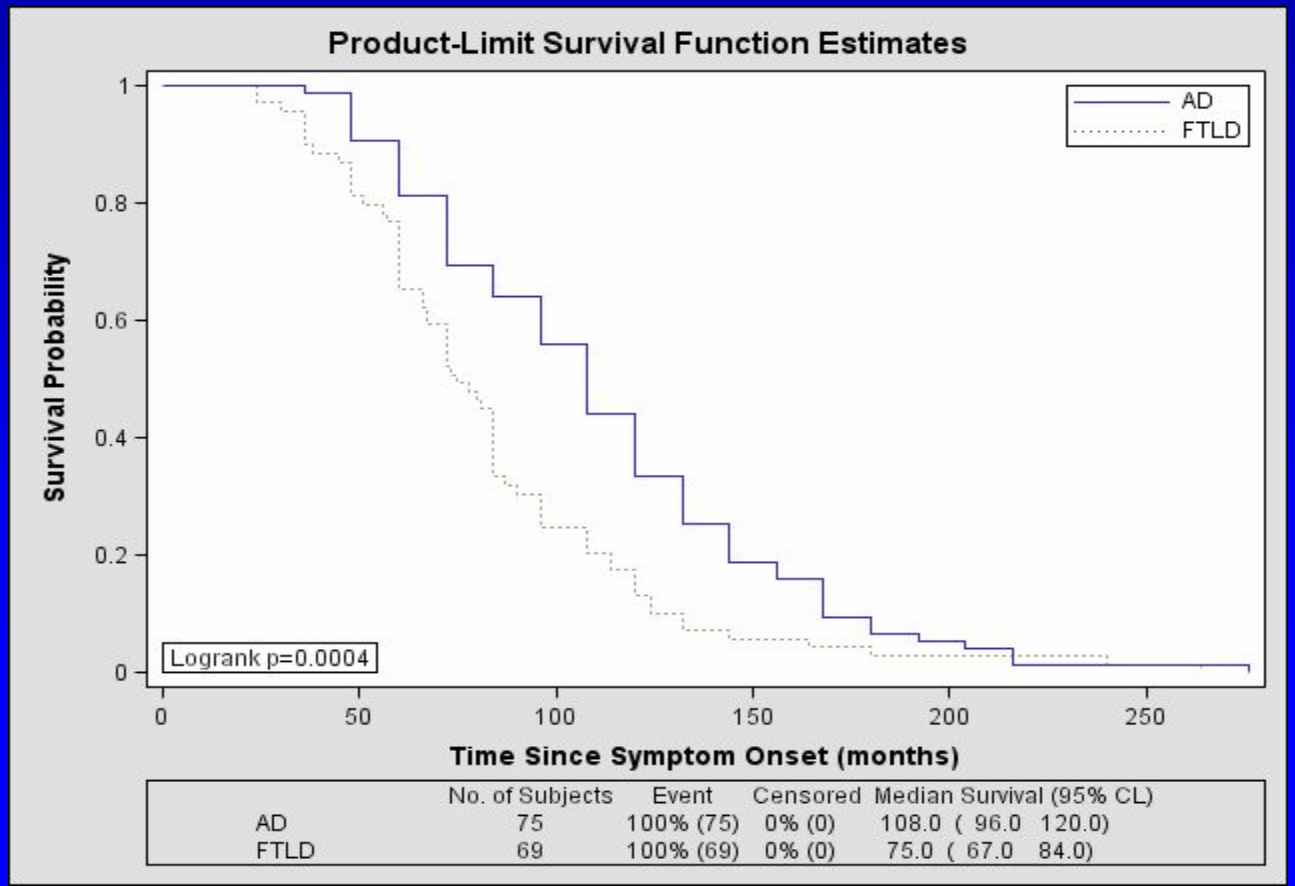
- Two major forms of pathology: tau-positive and tau-negative

Background

- FTLD progresses to death more rapidly than Alzheimer's disease (AD)
- No consensus on the factors contributing to rapid decline in FTLD

Background

Comparison of survival: AD vs FTLD



Objective

- Examine factors associated with survival in autopsy-confirmed FTLD

Background: Literature Review

Previous assessments of survival in FTLD:

- Longer survival in tau-positive (Hodges, 2003; Roberson, 2005)
- Equal survival in tau positive + tau negative (Rascovsky, 2005; Josephs, 2005; Kertez, 2005)

Distinct Features of Our Study

- Largest cohort of autopsy-proven FTLD
- Use empirical measure of the actual amount of pathology
- Multivariate analysis of a variety of factors

Study Cohort

Inclusion criteria:

- All patients with autopsy-proven FTLD identified at Penn from 1995-2005
- Clinical assessments at Penn or UCSF (N=91)

Study Cohort

Excluded:

- Patients without adequately detailed clinical evaluations (N=15)
- Patients with a clinical diagnosis of motor neuron disease (MND) (N=5).

Study Cohort

- Final analysis cohort included 71 patients with pathologically-proven FTLD.

Clinical and demographic characteristics of participants

Characteristics	Whole Cohort[4] (N=71)	Tau-negative Group (N=35)	Tau-positive Group (N=36)
Male, n (%)	**34 (48)**	**16 (46)**	**18 (50)**
Age at symptom onset (yrs)[1]	61.0 ± 9.5 (30-80)	60.4 ± 9.5 (43-80)	61.5 ± 9.7 (30-80)
Education (yrs)[1,2]	15.0 ± 2.8 (10-20)	14.8 ± 2.6 (10-20)	15.1 ± 3.0 (10-20)
MMSE at initial clinic visit[1,2]	23.0 ± 6.8 (4-30)	22.8 ± 6.2 (8-30)	23.2 ± 7.3 (4-30)
Presence of family history, n (%)[3]	**30 (47)**	**16 (52)**	**14 (42)**

Survival Time

- Computed from time of symptom onset until death.
  - Symptom onset based on family report of the earliest persistently-abnormal clinical feature

Clinical Signs from Neurological Exam

- Social dysfunction
- Aphasia
- Extrapyramidal features
- Pyramidal signs

Neuropsychological Tests

- Mini-Mental State Examination (MMSE)
- Boston Naming Test
- Animal Fluency
- Word List Recall
- Digit Span Forward

Other factors

- Family history
- Tau haplotype
- Apolipoprotein E genotypic information

Pathology Evaluation

- Semi-quantified Neuropathologic assessment:
  -Tau
  -Amyloid
  -Ubiquitin
- Semi-quantitative grading
  - 0=no or rare pathology
  - 1=low pathology
  - 2=moderate pathology
  - 3=high pathology

Pathology Evaluation: Brain Regions Examined

- Mid-frontal gyrus
- Inferior parietal lobule
- Superior and middle temporal gyri
- Anterior cingulate gyrus
- Hippocampus and entorhinal cortex
- Amygdala
- Thalamus
- basal ganglia

Dichotomized Neuropathology Variables

- Low pathology (grading = 0 or 1)
- Abundant pathology (grading =2 or 3)
- Cases with low tau pathology are referred to as *tau-negative* (average tau pathology rating ≤ 1)
- Cases with abundant tau pathology are referred to as *tau-positive* (average tau pathology rating ≥ 2)

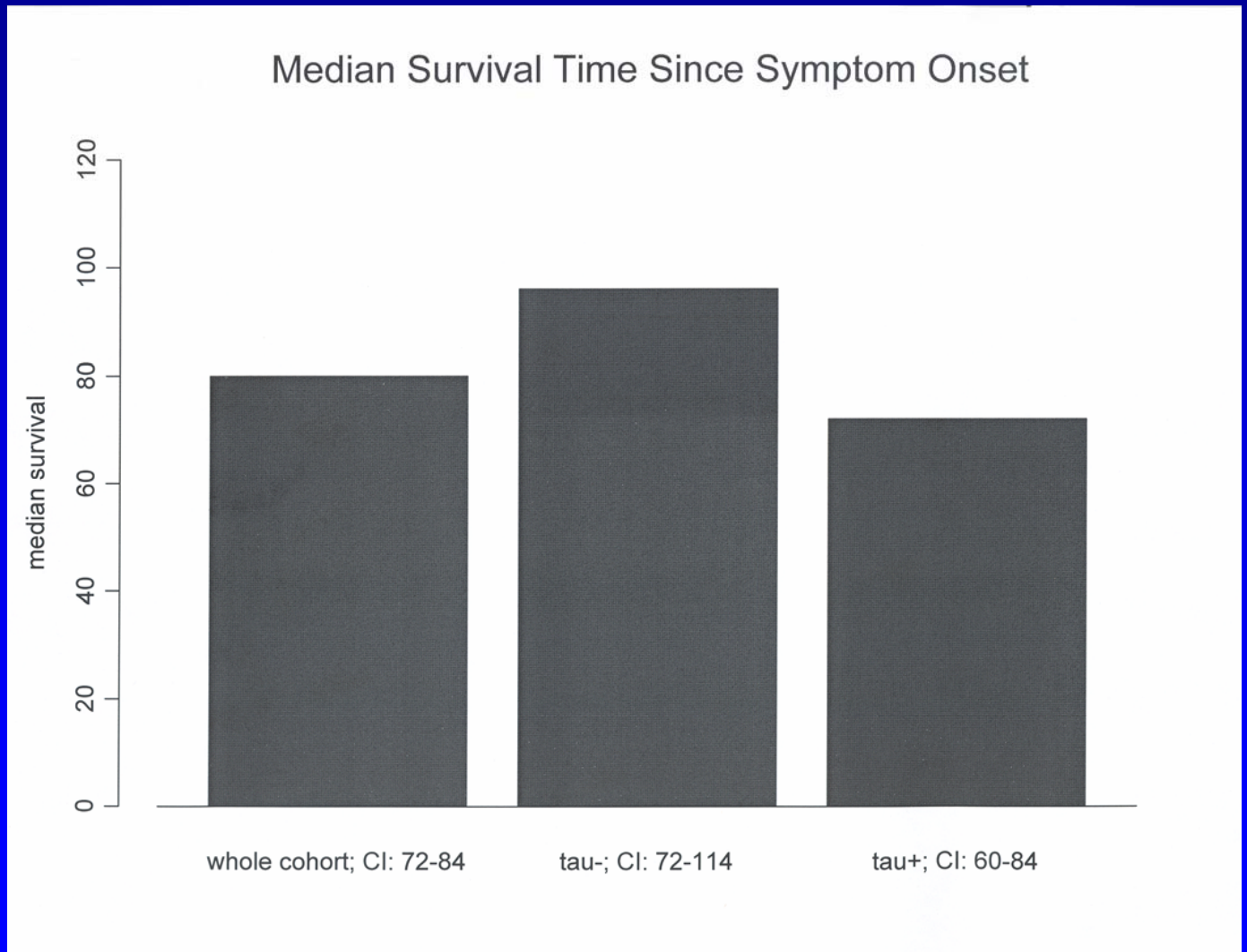
Pathology Variables Used in Analyses

- Average pathology across all regions for each ascertained protein
- Average pathology reading across tau, ubiquitin, and amyloid for a single brain region

Statistical Analyses

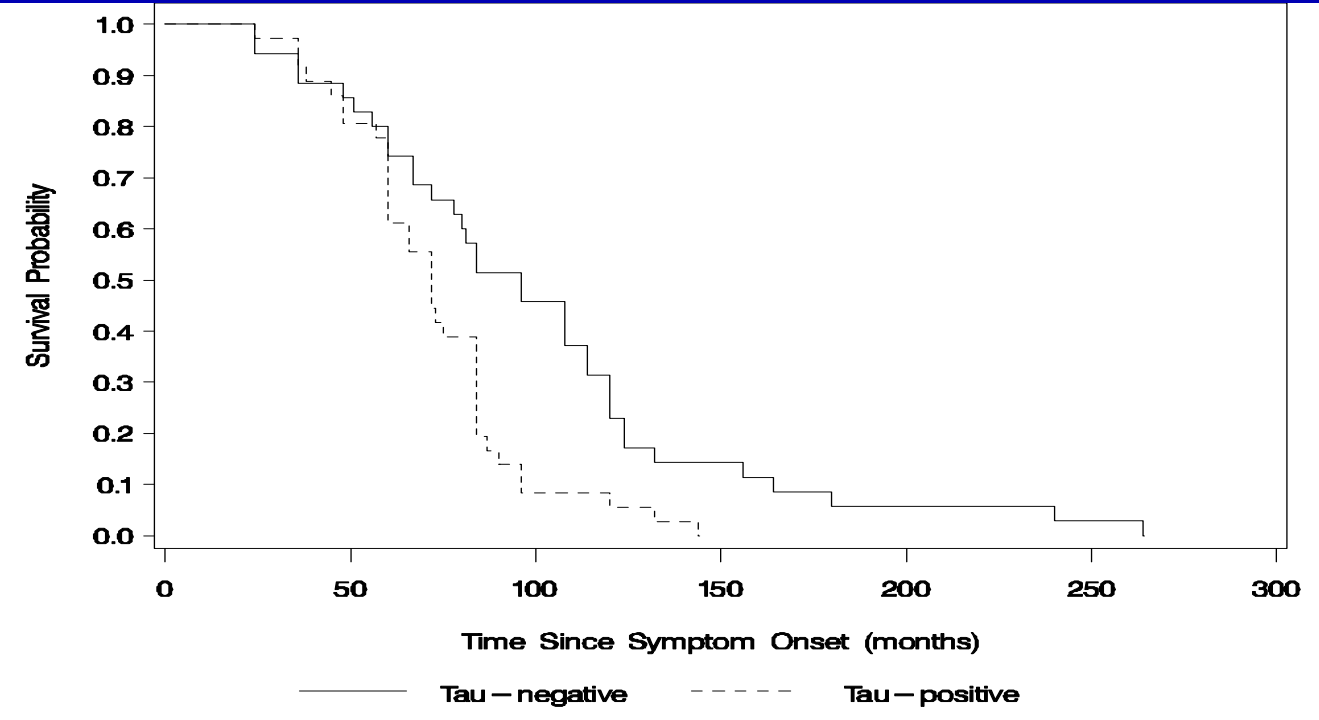
- Survival probabilities from Kaplan-Meier method
- Factors associated with survival from single and multiple covariate Cox proportional hazards regression models:
  - Demographic features
  - Clinical features at the initial visit
  - Neuropsychology variables
  - Family history
  - Genetic
  - Neuropathology features

Results


Median Survival Time Since Symptom Onset
median survival
0
20
40
60
80
100
120
whole cohort; CI: 72-84
tau-; CI: 72-114
tau+; CI: 60-84

Univariate Factors

- tau-positive pathology had shorter survival than negative pathology
- Hazard ratio of dying = 2.003, 95% CI = 1.209-3.318, p = 0.007



Univariate Factors

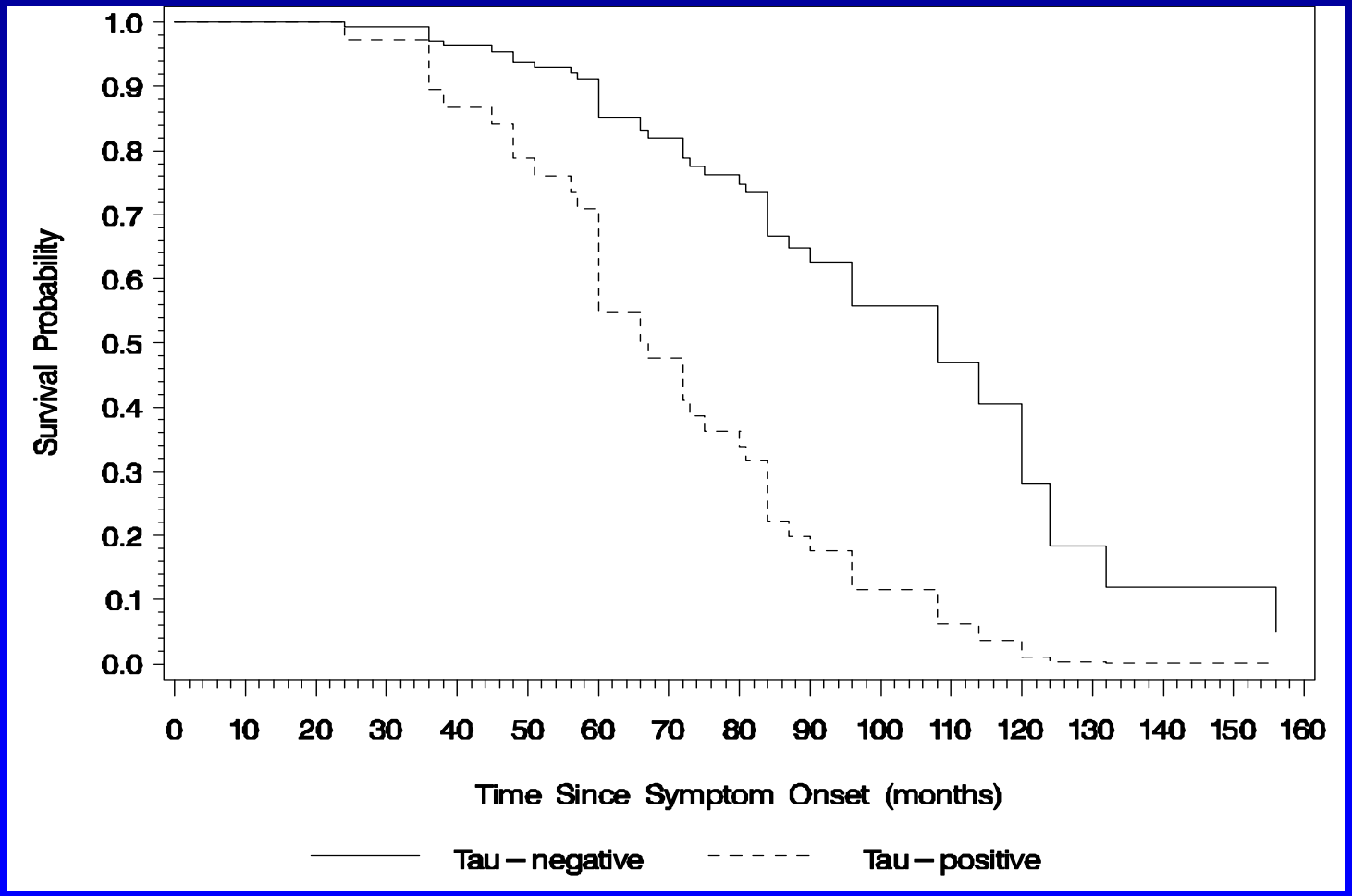
Shorter survival time was associated with:

- pathology of any sort in basal ganglia
- pathology of any sort in anterior cingulate
- tau-positive pathology in all cortical region

Multivariate analysis

- Tau Pathology (HR = 3.750, 95% CI: 1.694-8.303; p = 0.001)
- Adjusting for
  - years of education
  - pathology of any sort in basal ganglia

Survival Curves in Tau Pathology Sub-Groups Adjusted for Years of Education and Average Pathology in Basal Ganglia



Discussion: Discrepancies with Other Findings

Some studies have found that tau-negative pathology was associated with shorter survival:

- Previous studies performed only univariate analyses
- Our study used actual empirical burden of tau pathology
- Our cohort had many corticobasal degeneration patients, while other studies had many tau-positive patients with Pick's disease

Conclusion

- Tau-positive pathology represents a significant risk to survival in FTLD

Reference

- **Xie SX**, Forman MS, Farmer J, Moore P, Wang Y, Wang X, Clark CM, Coslett HB, Chatterjee A, Arnold SE, Rosen H, Karlawish JHT, Van Deerlin VM, Lee VM-Y, Trojanowski JQ, Grossman M. Factors associated with survival probability in autopsy-proven frontotemporal lobar degeneration. *Journal of Neurology, Neurosurgery & Psychiatry* (accepted for publication, 2007).