

MAYO CLINIC

Evaluating the Diagnostic Utility of CSF Protein 14-3-3 for Prion Disease in the Modern Era

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INTRODUCTION

CSF protein 14-3-3 has long been included within diagnostic criteria for prion disease endorsed by major international organizations^{1,2}. Advances in MRI and the advent of RT-QuIC assays capable of detecting prions in CSF have enabled detection of prion disease at earlier stages, when markers of neuronal injury such as 14-3-3 may be undetectable³. However, the clinical utility of this diagnostic biomarker amidst improvements MRI markers and RT-QuIC testing for prion disease is unclear.

OBJECTIVE

To evaluate the real-world diagnostic utility of cerebrospinal fluid (CSF) protein 14-3-3 for prion disease in the modern diagnostic era.

METHODS

- We analyzed CSF biomarker data from 629 participants evaluated at academic centers (Washington University in St. Louis and Mayo Clinic; 2016–2025) for prion disease (definite, n=9; probable, n=37), non-prion rapidly progressive dementia (RPD; n=147), and typically progressive dementia (n=436). Participants with RPD developed dementia (global CDR ≥ 1) within one year or complete functional dependence (CDR ≥ 2) within two years of symptom onset
- Biomarkers were measured using standardized NPDPS protocols, including RT-QuIC assays and ELISA measures of 14-3-3 and total tau. Brain MRIs were assessed for prion-associated changes
- Diagnostic performance was summarized using sensitivity, specificity, accuracy, and likelihood ratios. Survival associations were assessed using Cox models.

RESULTS

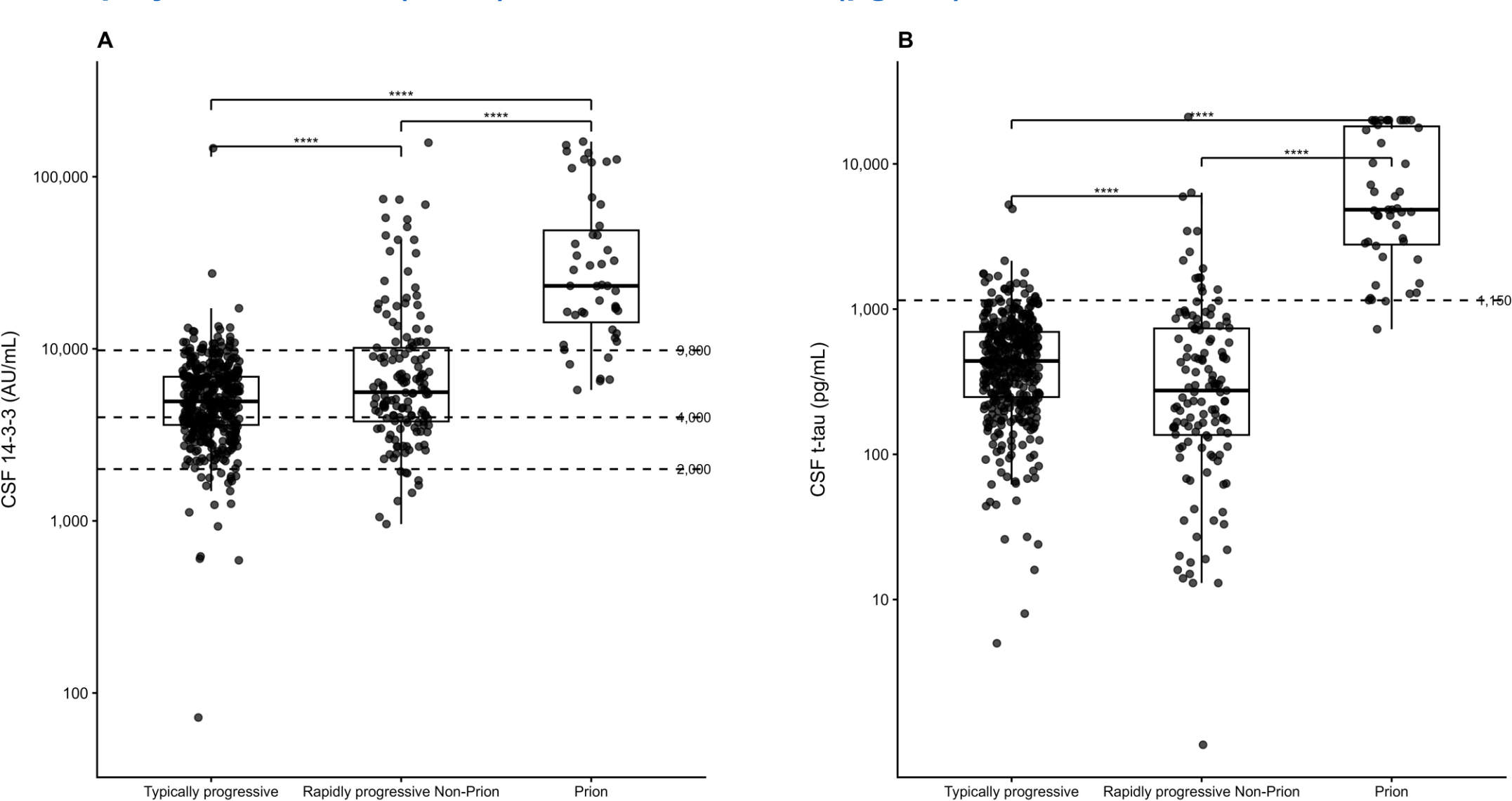
Table 1. Table.1 Baseline characteristics and clinical features of the included cohorts.

Variable	Typical (n=436)	CJD (n=46)	Rapid non-CJD (n=147)	Total (n=629)	P
Male	237 (54.4) ^a	29 (63.0) ^a	83 (56.5) ^a	347 (55.2)	0.80
Black	12 (2.8) ^a	0 (0.0) ^b	21 (14.3) ^a	33 (5.2)	<0.001
Non-Hispanic White	411 (94.3) ^a	44 (95.7) ^b	121 (82.3) ^a	576 (91.6)	<0.001
Hispanic White	11 (2.5) ^a	0 (0.0) ^a	0 (0.0) ^a	11 (1.8)	0.084
Age at symptom onset, y	67.5 (54.7–80.5) ^a	68.5 (54.1–85.4) ^a	68.2 (43.2–83.3) ^a	66.1 (18.4–86.4)	0.138
Age at CSF sampling, y	71.8 (57.8–83.7) ^{ab}	69.0 (54.2–87.0) ^b	68.9 (43.2–83.5) ^a	68.3 (18.6–87.9)	<0.001
Symptom duration, months	58.7 (51.4–67.0) ^a	10.7 (3.7–19.0) ^b	18.1 (8.3–30.4) ^c	65 (1.3–287.47)	<0.001

Groups with different superscript letters differ significantly.

Age at symptom onset and sex distribution were similar across groups, with slight male predominance (55.2%). Most participants were non-Hispanic White (89.8%).

Figure 1. Scatterplot of CSF 14-3-3 and total tau Levels Across etiologic diagnoses A. displays CSF 14-3-3 (U/mL) B. total tau Levels (pg/mL)



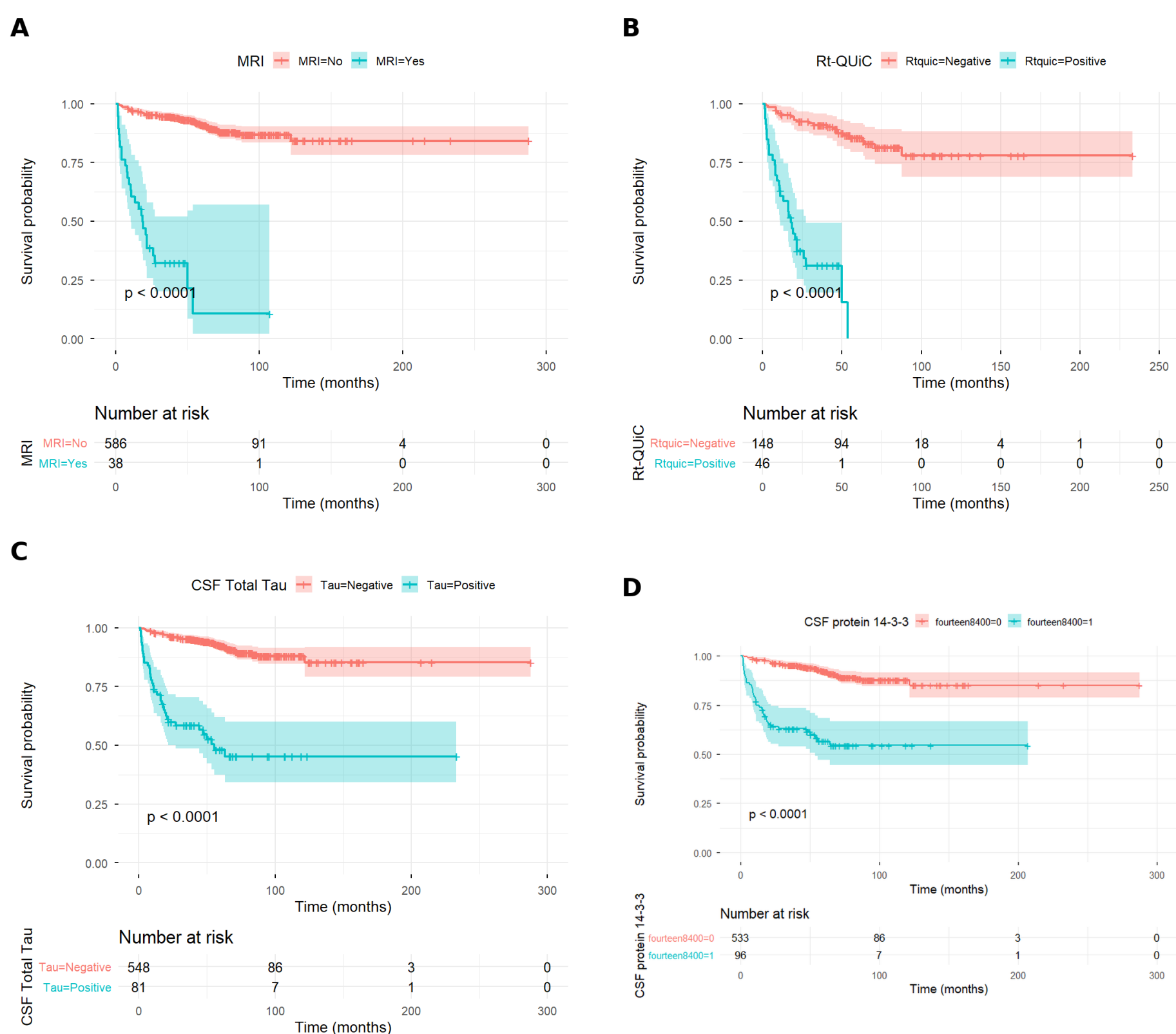
Elevated levels of CSF 14-3-3 protein and CSF total tau were common in patients with non-prion related causes of rapidly and typically progressive dementia. Prion disease was reliably distinguished from non-prion dementias by absolute levels of CSF 14-3-3 protein (mean difference: 37481.6 AU/mL) and total tau (mean difference: 8150 pg/mL).

Table 2. Diagnostic performance of CSF protein 14-3-3 across dementia subgroups .

(14-3-3 ≥ 2000 AU/mL)	Sensitivity	Specificity	Accuracy	LR+	LR-
Prion vs All Non-prion	100%	4.8%	11.8%	1.1	0
Prion vs Typical	100%	4.4%	13.5%	1.1	0
Prion vs Rapid Non-Prion	100%	6.1%	28.5%	1.1	0
RPD (Prion + Rapid) vs Typical	95.3%	4.4%	32.3%	1	1.1
Rapid non- Prion vs Typical	93.9%	4.4%	26.9%	1	1.4
(14-3-3 optimal cutoff ≥ 9800 AU)					
Prion vs All Non-prion	84.80%	90.20%	89.70%	8.65	0.17
Prion vs Typical	84.80%	95.20%	94.00%	17.7	0.16
Prion vs Rapid Non-Prion	84.80%	75.50%	77.20%	3.46	0.2
RPD (Prion + Rapid) vs Typical	38.90%	95.20%	77.80%	8.1	0.64
Rapid non- Prion vs Typical	24.50%	95.20%	77.30%	5.1	0.79

- CSF protein 14-3-3 demonstrated very high sensitivity FOR PRION DISEASE but extremely low specificity at the current threshold (≥ 2000 AU/mL) applied by the NPDPS. Marked improvement in specificity was observed when using an optimized cutoff of 9,800 AU/mL.
- CSF protein 14-3-3 demonstrated lower diagnostic accuracy (AUC = 0.84) compared with RT-QuIC (AUC = 0.98), CSF total tau (AUC = 0.93), and MRI (AUC = 0.91).

Figure 2. Kaplan–Meier Survival Curves by Biomarker Status



- Kaplan–Meier analyses showed no survival differences at the revised CSF 14-3-3 threshold ($\geq 2,000$ AU/mL; log-rank p=0.06). Higher thresholds ($\geq 4,000$ and $\geq 10,400$ AU/mL) demonstrated clear prognostic separation (both p<0.001). MRI, RT-QuIC, and CSF total tau consistently identified participants with shorter symptomatic duration (all p<0.001).
- In multivariable logistic regression, age and CSF total tau levels—not diagnosis—were independently associated with 14-3-3 positivity.

SUMMARY

- Plasma at the revised threshold ($\geq 2,000$ AU/mL), CSF protein 14-3-3 showed high sensitivity (100%) but very low specificity ($\leq 6.1\%$) and low accuracy ($\leq 28.5\%$), with positive likelihood ratios approximating 1 means that a positive test result does not meaningfully change the probability of disease.
- Elevated CSF Protein 14-3-3 levels were common in patients with other (non-prion) causes of rapidly (93.9%) and typically progressive dementia (95.6%).
- In contrast, CSF total tau levels ($\geq 1,150$ pg/mL), RT-QuIC assays, and MRI showed high diagnostic accuracy for detection of prion disease.
- Higher 14-3-3 concentrations were modestly associated with shorter survival, although associations attenuated after adjustment for total tau.

CONCLUSION

CSF protein 14-3-3 provides minimal incremental clinical value for the diagnosis of prion disease compared with RT-QuIC, CSF total tau, and MRI.

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