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## INTRODUCTION

Progression independent of relapse activity (PIRA) is a major driver of long-term disability in multiple sclerosis (MS). Conventional MRI markers only partly explain this process. The choroid plexus (ChP), a key interface between CNS and immune system, has recently been implicated in smoldering inflammation. ChP enlargement may therefore represent a novel MRI biomarker to identify patients at higher risk of PIRA.

## METHODS

**Study design:** Observational cohort study with 96 relapsing MS patients, followed for 8 years.

**Clinical assessment:** Expanded Disability Status Scale (EDSS) performed at baseline and during follow-up. PIRA was defined as a 6-month confirmed EDSS increase of 1.5, 1.0, or 0.5 points, depending on baseline EDSS.

**MRI baseline measures:**

- White matter lesion number and volume
- Cortical lesions
- Thalamic volume
- Global cortical thickness
- Spinal cord lesions
- **Choroid plexus volume**, normalized to intracranial volume, automatically segmented with ASCHOPLEX, a validated deep-learning tool (Visani et al, *Comput Biol Med* 2024).

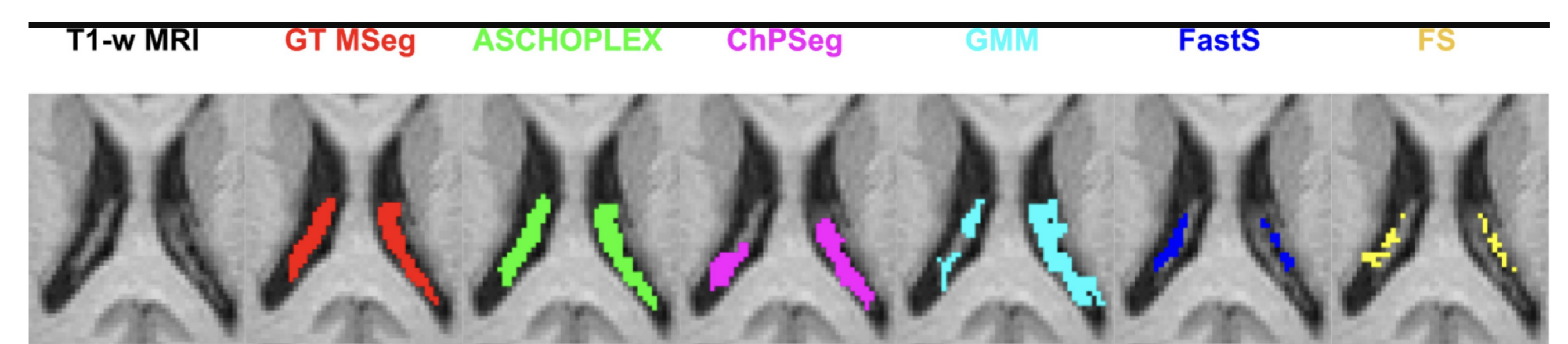
**Statistical analysis:** Logistic regression models assessed predictors of PIRA. Discriminative accuracy was evaluated by ROC curve analysis.

### Baseline characteristics<sup>1</sup>

Overall vs No PIRA vs PIRA

	Overall	No PIRA	PIRA	p-value
<b>Clinical</b>				
EDSS (T0)	2.00 (1.00–2.62)	2.00 (1.00–2.00)	3.00 (2.00–4.00)	<0.001
<b>Demographics</b>				
Age (years)	36.81 (28.16–46.37)	33.46 (27.29–42.35)	44.92 (35.72–49.11)	0.007
<b>MRI</b>				
Choroid plexus volume (CPV)	1.65 (1.43–2.00)	1.59 (1.38–1.90)	1.92 (1.67–2.11)	<0.001
Cortical lesion number	2.00 (0.00–6.00)	2.00 (0.00–5.00)	5.00 (0.00–8.50)	0.019
Cortical lesion volume (cm <sup>3</sup> )	160.00 (0.00–570.75)	136.00 (0.00–435.00)	422.00 (0.00–677.00)	0.027
T2 lesion number	8.00 (6.00–11.00)	8.00 (7.00–11.00)	8.00 (5.25–11.75)	0.929
T2 lesion volume	819.00 (531.00–1157.50)	785.00 (456.00–1092.00)	890.00 (666.00–1344.00)	0.323

<sup>1</sup> Continuous: median (IQR). Categorical: n (%). Tests: Wilcoxon rank-sum (continuous), Fisher's exact (categorical).



Comparison of Choroid Plexus predicted segmentation. From left to right, the figure shows a zoom-in of the 3D T1-w MRI with superimposed manual segmentation (GT MSeg) in red, proposed method ASCHOPLEX in green, FastSurfer (FastS) in blue, ChPSeg in pink, Gaussian Mixture Model (GMM) in light-blue, and FreeSurfer (FS) in yellow. Percentage Volume Difference metric (reference GT MSeg): ASCHOPLEX +0.32%, ChPSeg +5.92%, FS -48.79%, FastS -40.79%, GMM +19.52%

## AIM OF THE STUDY

To determine whether baseline choroid plexus (ChP) volume, compared with conventional MRI metrics, predicts long-term disability progression independent of relapse activity (PIRA).

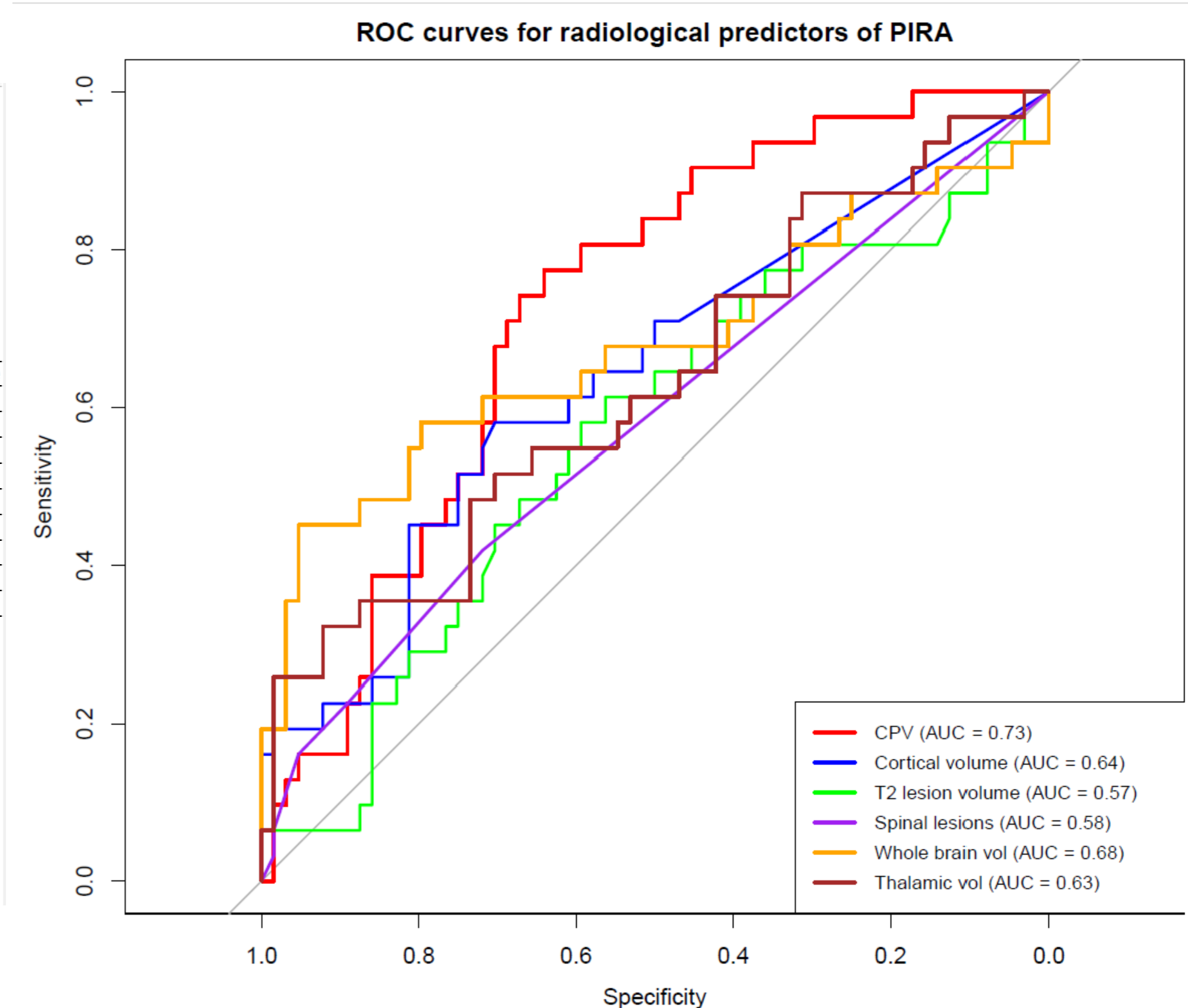
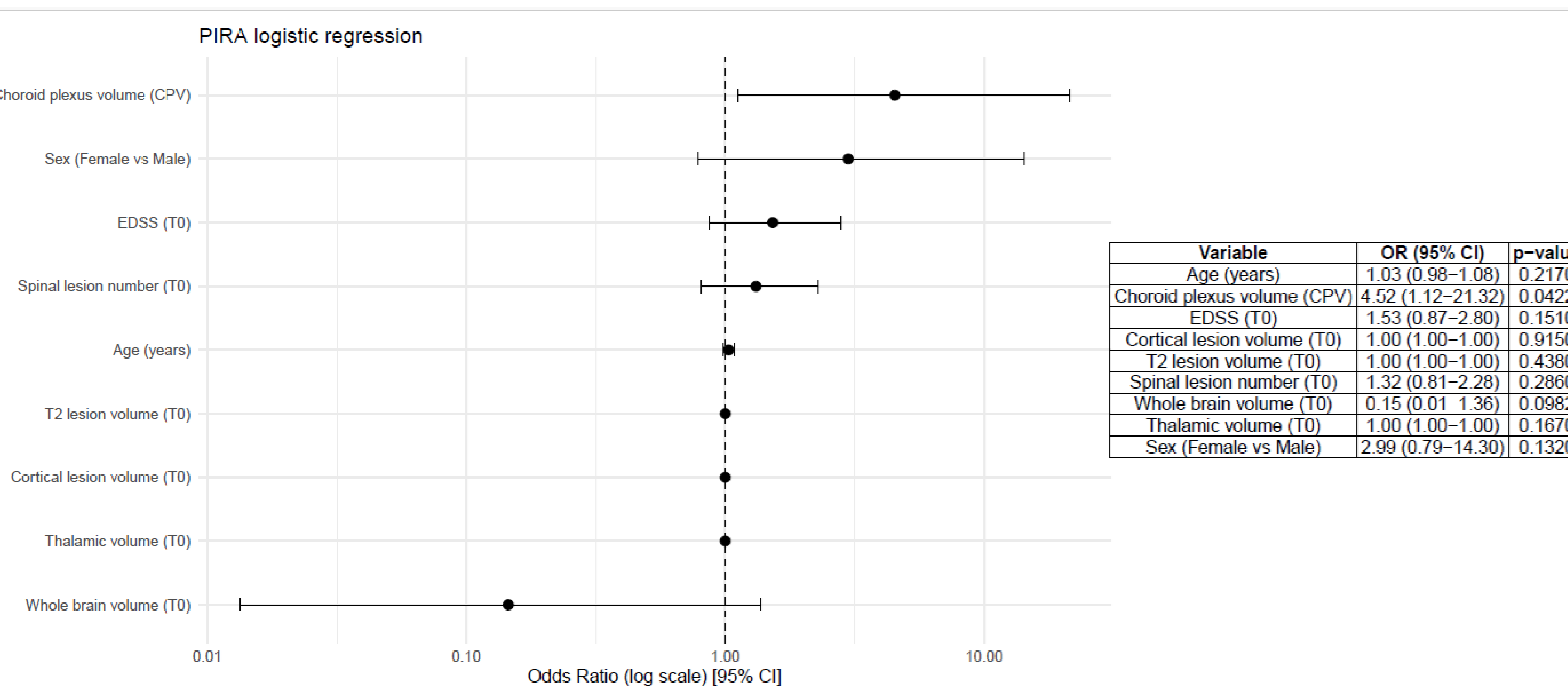
## RESULTS

Ninety-six patients with relapsing MS were followed for a median of 8 years. At baseline, the median age was 36.8 years (IQR 28.2–46.4) and the median EDSS was 2.0 (IQR 1–3). During follow-up, PIRA occurred in 31 patients (32%).

Patients who developed PIRA were significantly older at diagnosis ( $44.9 \pm 6.7$  vs  $33.5 \pm 7.6$  years,  $p=0.007$ ) and had a higher baseline disability (EDSS  $3.0 \pm 1.0$  vs  $2.0 \pm 0.8$ ,  $p<0.001$ ) compared with those without PIRA. Importantly, they also showed a greater choroid plexus (ChP) volume at baseline ( $1.92 \pm 0.21$  mL vs  $1.59 \pm 0.26$  mL,  $p<0.001$ ).

In multivariate logistic regression analysis, **normalized ChP volume was the only independent predictor of PIRA** (OR 4.52, 95% CI 1.12–21.32,  $p=0.042$ ). Other MRI parameters—including white matter lesion volume, cortical lesion volume, thalamic volume, spinal lesion number, and whole brain volume—did not reach statistical significance. Notably, baseline EDSS and age also failed to predict PIRA when included in the model.

Receiver-operating characteristic (ROC) curve analysis confirmed the **highest discriminative accuracy for ChP volume** among all tested MRI metrics (AUC=0.73).



## CONCLUSIONS

- Baseline normalized ChP volume was the only independent predictor of PIRA, outperforming conventional MRI markers.
- ChP enlargement likely reflects persistent inflammatory mechanisms driving disability progression.
- Its integration into baseline MRI protocols may support early risk stratification and personalized treatment in MS.

## DISCLOSURES

Disclosures: Monica Sicchieri: nothing to disclose; Damiano Marastoni: received research support and/or honoraria for speaking and funds for travel from Roche, Sanofi-Genzyme, Merck-Serono, Biogen Idec, and Novartis and receives research support from Italian Minister of Health; Giuseppe Schirò: nothing to disclose; Agnese Tamanti: received research support from Merck; Valentina Visani: nothing to disclose; Daniela Anni: nothing to disclose; Stefano Ziccardi: nothing to disclose; Valentina Camera: received research grant from European Charcot Foundation, received support for scientific meetings from Biogen, Janssen, Novartis, BMS, Roche, Alexion and speaking honoraria from Novartis and Alexion; Francesca Benedetta Pizzini: nothing to disclose; Roberta Magliozzi: nothing to disclose; Marco Castellaro: nothing to disclose; Massimiliano Calabrese: received speaker honoraria from Biogen, Bristol Myers Squibb, Celgene, Genzyme, Merck Serono, Novartis, and Roche and received research support from the Progressive MS Alliance, Italian Minister of Health, the Novartis Pharma, Roche, Bristol Myers Squibb and Merck Serono.