

Serum Markers of Cerebrovascular Injury correlate with Cognitive Decline and Alzheimer’s Pathology in the presence of BBB Breakdown

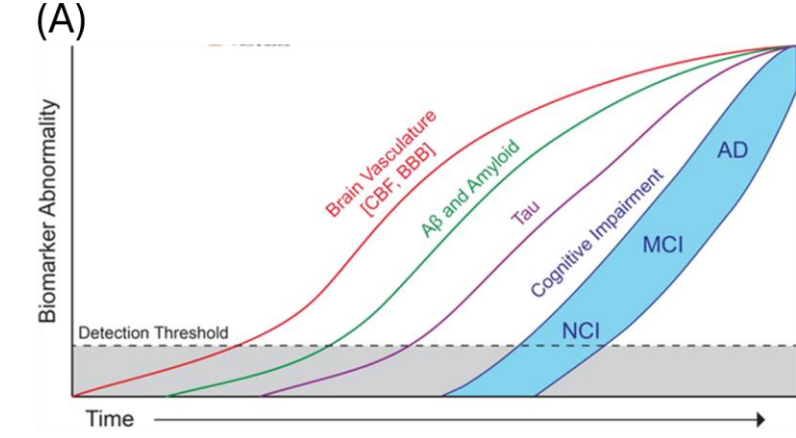
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Most serum markers of neurovascular injury correlated only weakly with cognitive decline and Alzheimer’s disease pathology. However, in the presence of BBB breakdown, the relationships were stronger. Serum PIGF and SLC6A12 correlated with cognitive decline in the absence of BBB breakdown and have potential as early-stage predictors of cognitive decline and ADNC before BBB breakdown in AD.

INTRODUCTION

Reduced cerebral blood flow and BBB breakdown are early pathological features of Alzheimer’s disease (AD). Cerebral small vessel disease (cSVD) contributes to ~45% of dementia cases and accelerates the onset of cognitive decline and disease progression in AD (Fig. 1).

(A) 

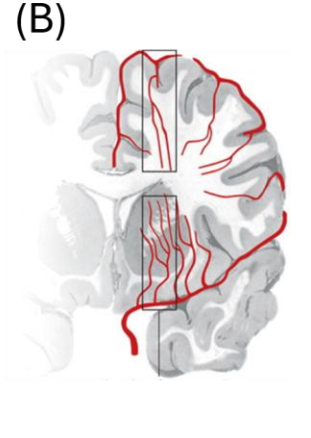
(B) 

Figure 1. AD has a long prodromal phase during which cerebral blood flow and BBB breakdown are early pathological features

METHODS

A panel of neurovascular markers and Qalb was measured by ELISA in 75 matched CSF and serum samples from cognitively unimpaired (CU), mildly cognitively impaired (MCI), and Alzheimer’s disease donors (25 per group) from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) study (Table 1).

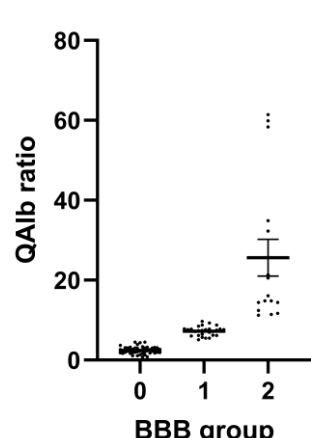
Demographics	CU	MCI	AD	P
Number	25	25	25	-
Age	69.5 ± 5.3	71.7 ± 6.9	73.0 ± 9.1	0.23
Male/Female	10/15	13/12	15/10	NS
APOE ε4 carriers, n (%)	2/25 (8)	14/56	18/72	p < 0.0001
Pathology markers	CU	MCI	AD	
CSF Aβ40 (pg/mL)	17,549.6 ± 4493.0	18,340.0 ± 5179.9	18,880.8 ± 5106.7	NS
CSF Aβ42 (pg/mL)	1514.6 ± 574.2	964.8 ± 486.2	580.5 ± 117.4	p < 0.0001
CSF total tau (pg/mL)	183.1 ± 37.4	274.1 ± 73.6	405.6 ± 117.2	p < 0.0001
CSF p-tau (pg/mL)	15.3 ± 2.9	26.4 ± 9.9	43.7 ± 16.5	p < 0.0001
PET Aβ+	0/24	18/25	25/25	p < 0.0001
PET Aβ (Centroids)	1.9 ± 8.9	48.2 ± 37.6	107.5 ± 30.4	p < 0.0001
PET tau (SUVR)	1.1 ± 0.2	1.29 ± 0.1	1.6 ± 0.1	p < 0.0001
Cognitive assessment	CU	MCI	AD	
CDR-M (0.5-1.2)	24/01/00	10/14/01	02/11/12	p < 0.0001
CDR-C (0.5-1.2)	24/01/00	10/14/01	02/17/06	p < 0.0001
CDR-SBR (mean ± SD)	0.0 ± 0.2	1.0 ± 1.4	2.8 ± 2.0	p < 0.0001
MoCA (mean ± SD)	26.3 ± 2.5	23.8 ± 4.6	19.0 ± 4.8	p < 0.0001
MMSE (mean ± SD)	29.3 ± 1.0	28.6 ± 1.7	23.8 ± 3.7	p < 0.0001
ADAS-COG (mean ± SD)	4.9 ± 1.8	8.2 ± 5.8	16.8 ± 9.5	p < 0.0001
ADAS-13 (mean ± SD)	7.1 ± 2.8	13.2 ± 8.7	25.7 ± 12.7	p < 0.0001

Table 1: Summary of the ADNI cohort with matched CSF and serum

RESULTS

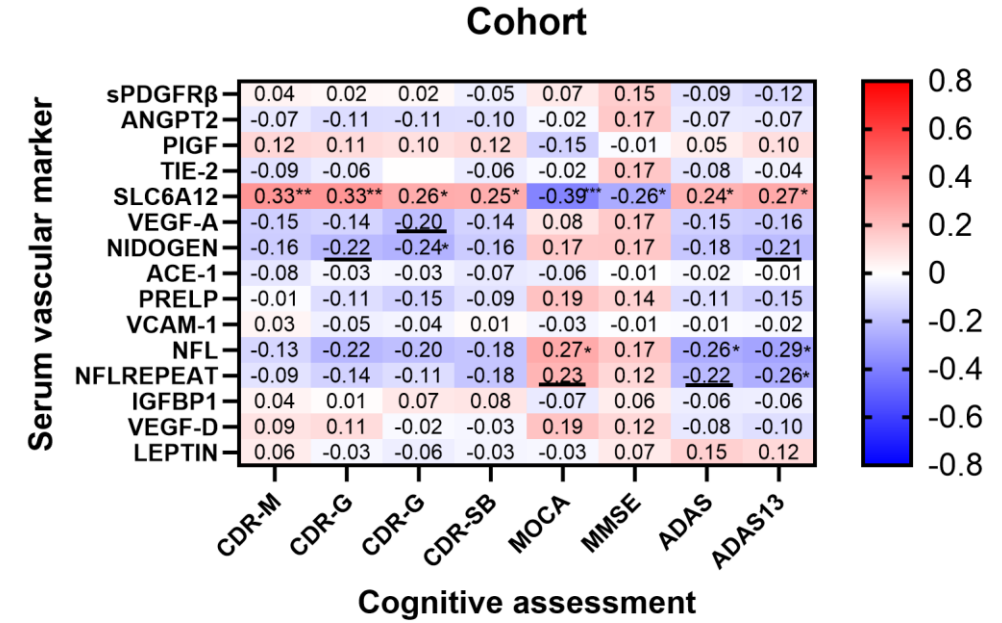
The cohort was stratified according to Qalb into: no BBB breakdown (Qalb < 5) n = 39, mild-moderate BBB breakdown (Qalb 5-10) n = 22, and severe BBB breakdown (Qalb > 10) (Figure 3).

Figure 3. Serum and CSF albumin levels were measured by ELISA and used to calculate the Qalb ratio.



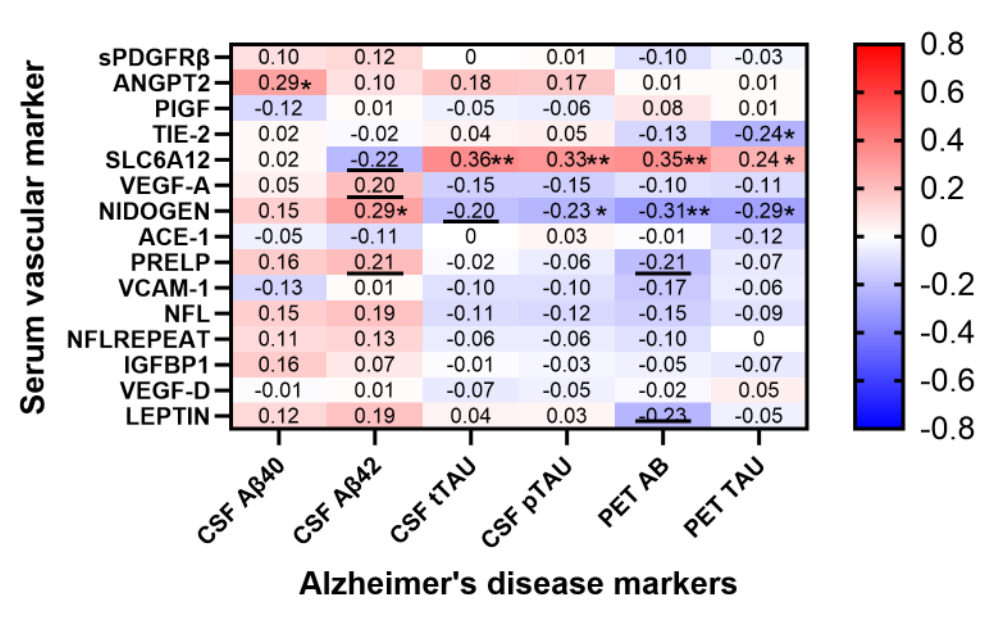
Serum markers of cerebrovascular injury and cognitive decline were weak/absent across the cohort (Figure 4).

Figure 4. Heatmap showing correlations between serum Markers of neurovascular injury and cognitive assessment



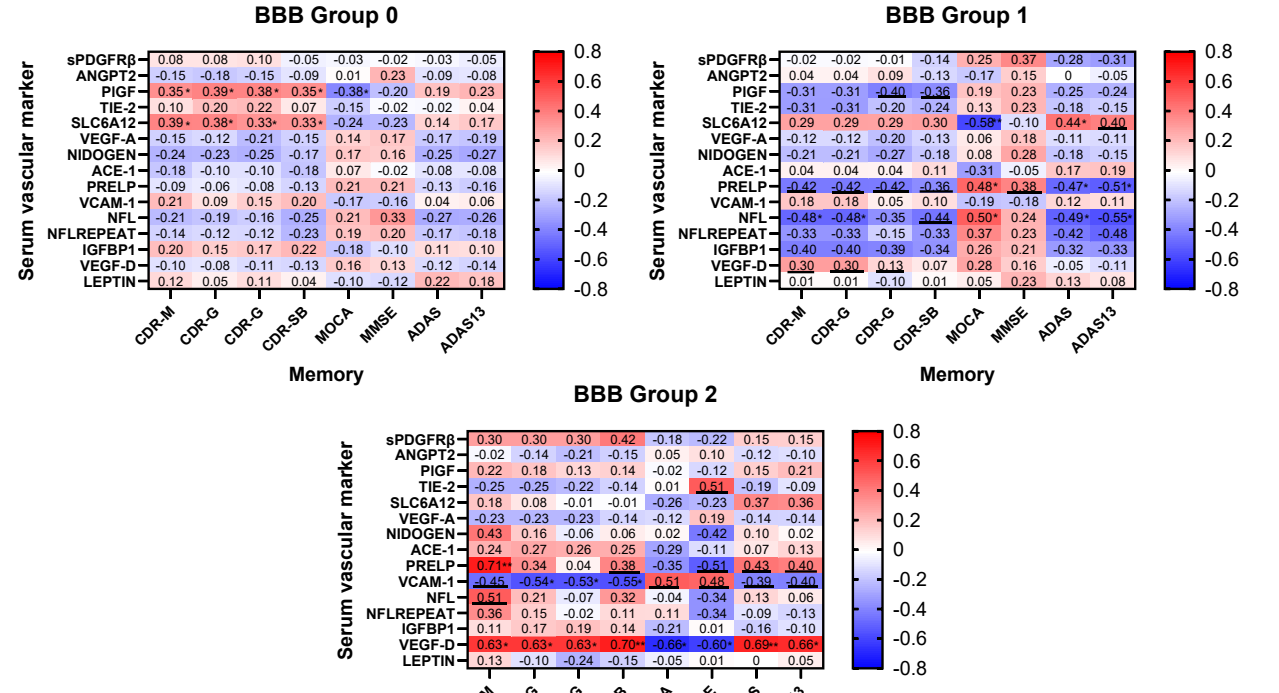
Serum markers also correlated weakly with markers of Alzheimer’s disease pathology (Figure 5).

Figure 5. Heatmap showing correlations between serum markers of neurovascular injury and fluid and imaging markers of Alzheimer’s disease pathology



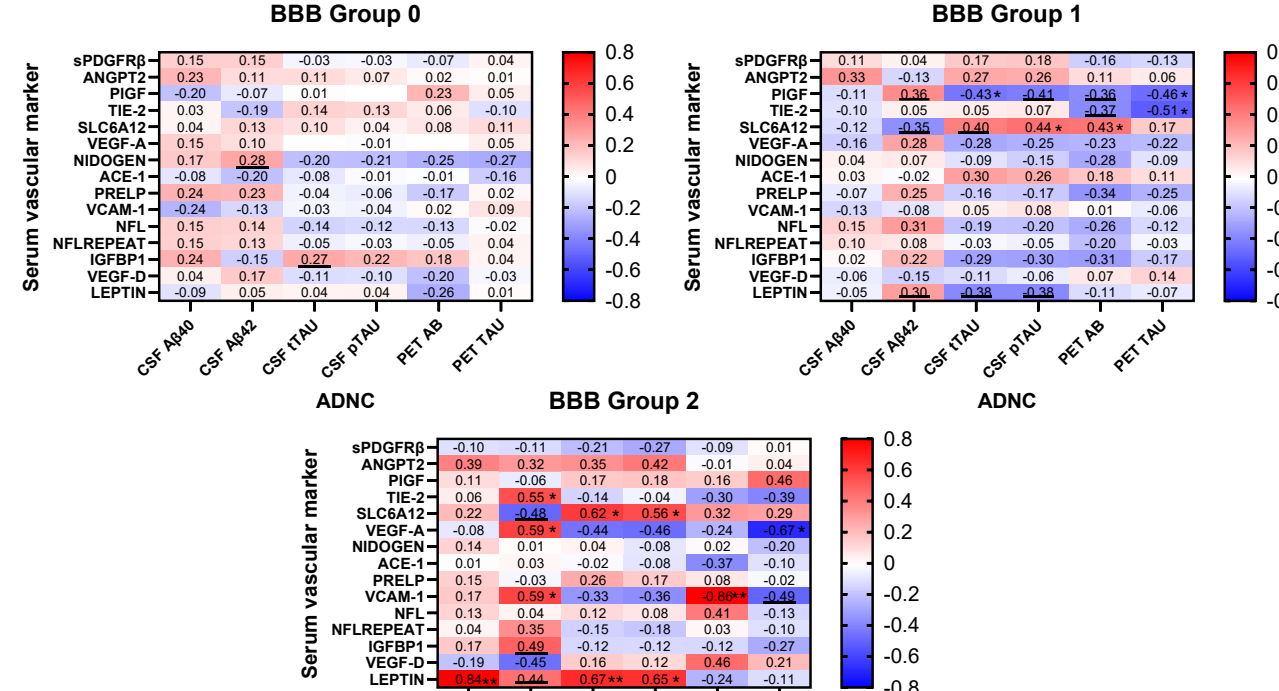
The relationships between serum markers of cerebrovascular injury and cognitive are modified severity of BBB leakiness (Figure 6).

Figure 6. Heatmaps showing correlations between serum markers of neurovascular injury and cognition in groups stratified by BBB breakdown severity



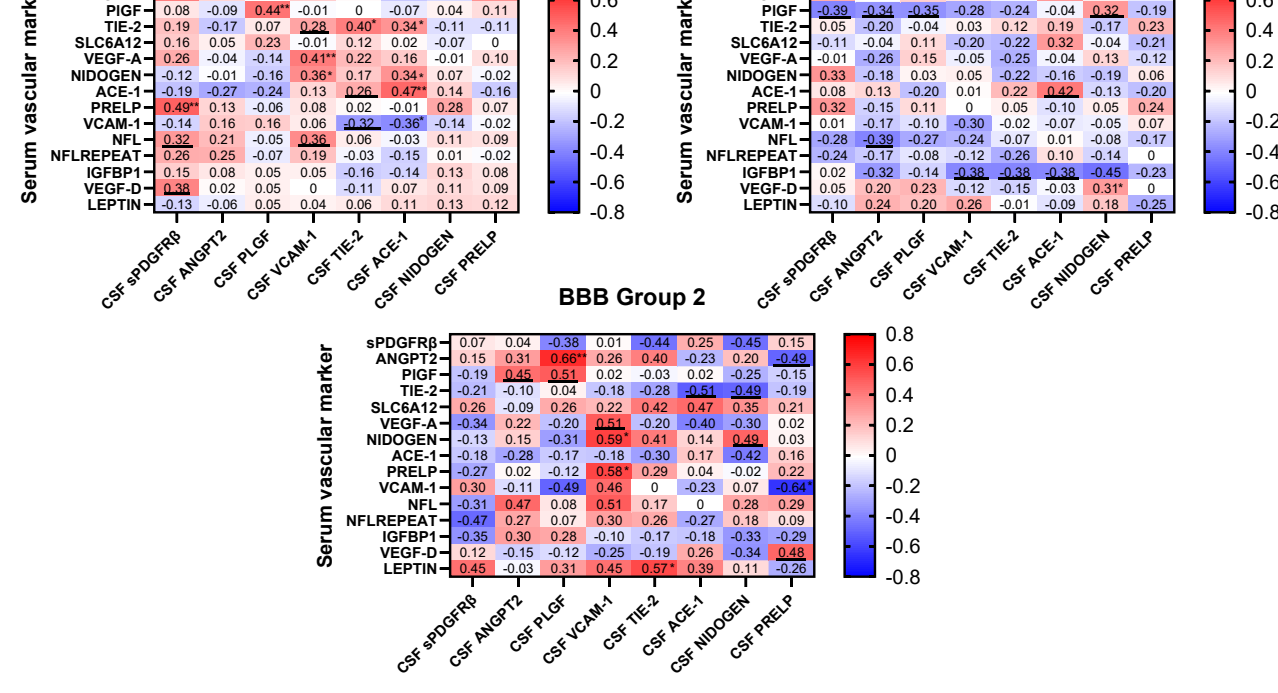
Serum cerebrovascular markers correlate with Alzheimer’s pathology in cases with BBB breakdown (Figure 7).

Figure 7. Heatmap showing correlations between serum markers of neurovascular injury and ADNC in groups stratified by BBB breakdown severity



Cerebrovascular markers in serum and CSF are modified by BBB severity (Figure 8).

Figure 8. Heatmaps showing correlations between markers of neurovascular injury in serum and CSF in relation to BBB leakiness



CONCLUSIONS

BBB breakdown modifies the relationships between serum and CSF markers of cerebrovascular injury and modifies their relationship to cognitive decline and ADNC.

(1): Miners JS, Roy G, Love S; the Alzheimer’s Disease Neuroimaging Initiative. CSF markers of vascular injury correlate with tau and cognitive decline in early Alzheimer’s disease. Alzheimers Dement. 2025 Dec;21(12):e70957. doi: 10.1002/alz.70957.

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