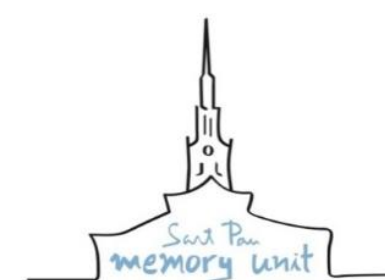


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Introduction/background

Blood biomarkers are increasingly used for the diagnosis and management of neurodegenerative diseases. Advances in analytical techniques now allow reliable detection of amyloid peptides, phosphorylated tau isoforms, and other markers of neuronal injury directly in plasma. However, these biomarkers are partially cleared through the kidneys, suggesting that renal function may represent an important confounding factor in their interpretation. Chronic kidney disease has been associated with increased levels of several biomarkers, raising concerns about potential diagnostic bias. In this context, biomarker ratios have been proposed as a strategy to mitigate such effects.

The aim of this study was to evaluate the impact of renal function, assessed by estimated glomerular filtration rate (eGFR) based on creatinine, on a broad panel of blood biomarkers of neurodegeneration, and to determine whether this impact affects their diagnostic performance for cerebral amyloidosis. Particular attention was given to the robustness of biomarker ratios.

Methods

This multicenter study included 420 patients from memory clinics enrolled in the ALZAN cohort. Patients were divided into three groups according to renal function: eGFR < 60, between 60 and 90, and above 90 mL/min/1.73m².

Plasma levels of Aβ40, Aβ42, p-tau181, p-tau217, neurofilament light chain (NfL), glial fibrillary acidic protein (GFAP), and brain-derived tau (BD-tau) were measured, along with several ratios including Aβ42/Aβ40 and p-tau217/Aβ42.

Associations between eGFR and blood biomarkers were evaluated using correlation and age-adjusted linear regression analyses.

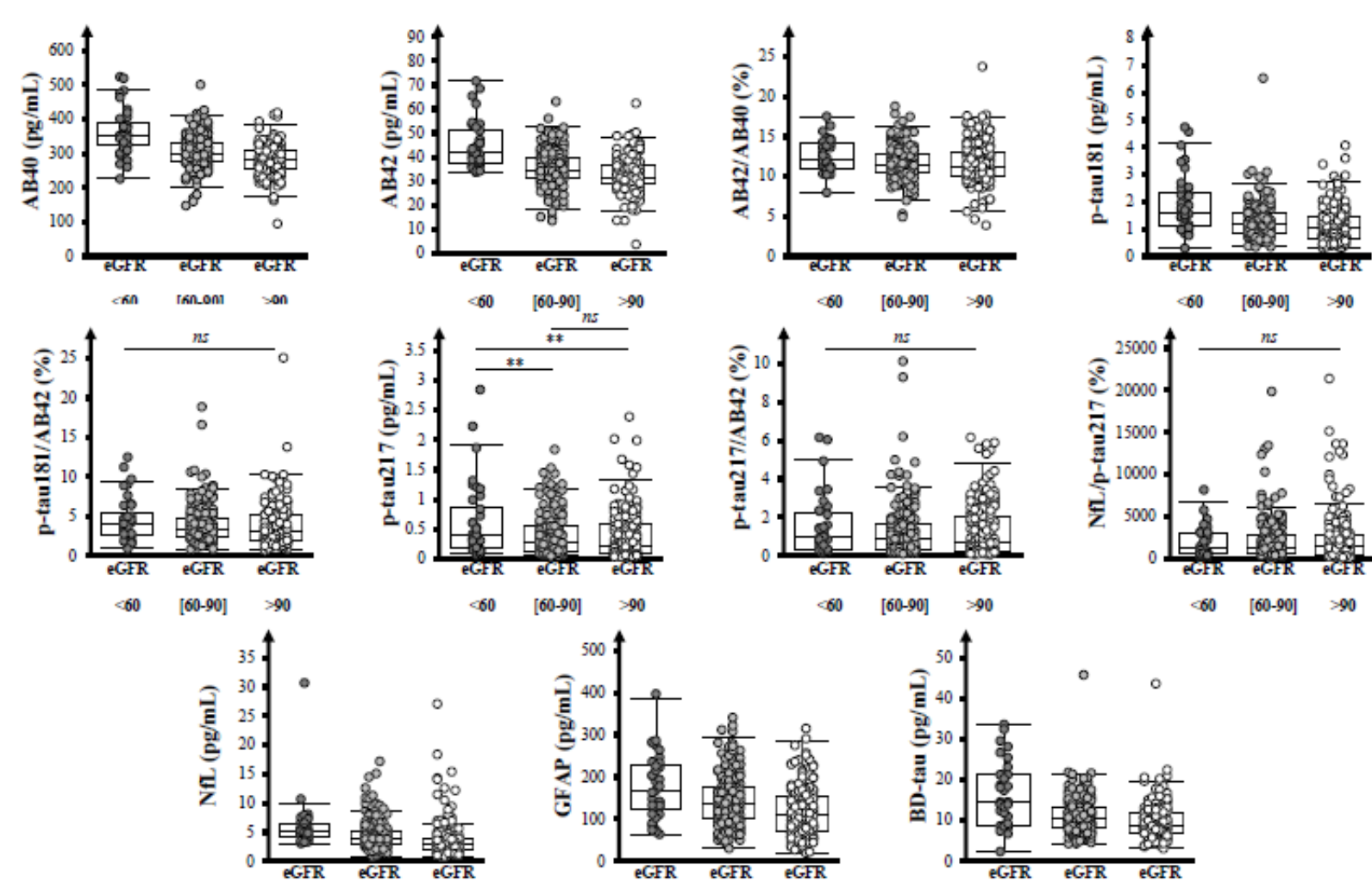
Diagnostic performances for cerebral amyloidosis, defined by a CSF Aβ42/Aβ40 ratio <7%, were assessed for individual biomarkers and biomarker ratios.

Results

A total of 420 patients were included and stratified according to renal function into three groups (eGFR <60, 60–90, and >90 mL/min/1.73m²). The groups were comparable in terms of sex distribution, body mass index, cognitive status, and cerebrospinal fluid biomarkers, although patients with lower eGFR were significantly older.

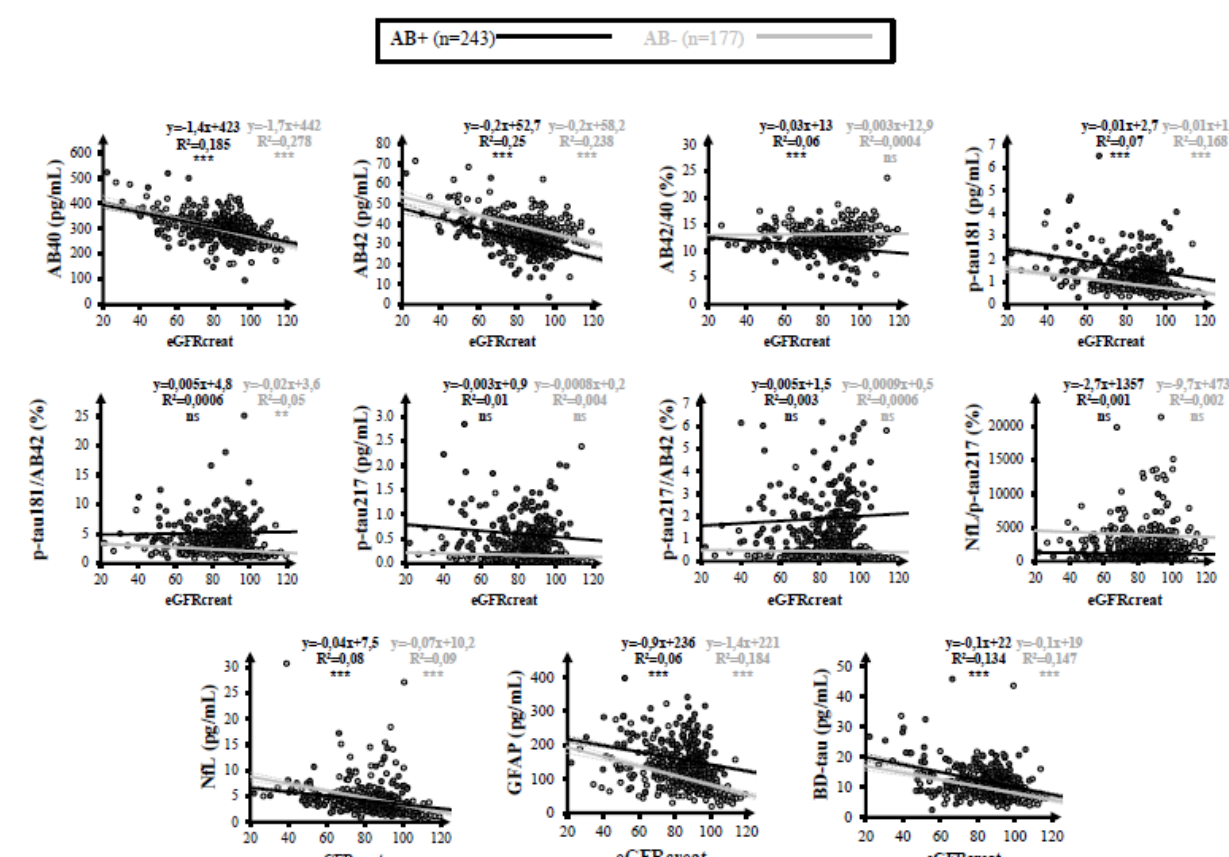
1- Impact of renal function on individual biomarkers

A strong effect of renal function on circulating biomarker concentrations was observed; all individual biomarkers exhibited higher mean levels in patients with impaired renal function. This increase was progressive, with the highest concentrations consistently observed in the eGFR <60 group. However, the magnitude and onset of this effect differed between biomarkers. Aβ40, Aβ42, NfL, GFAP, and BD-tau levels were significantly affected even by moderate decreases in renal function, with detectable increases already in the eGFR 60–90 group compared to eGFR >90. In contrast, p-tau181 and p-tau217 showed a significant increase only in patients with more severe renal impairment (eGFR <60), suggesting a differential sensitivity to renal clearance mechanisms.

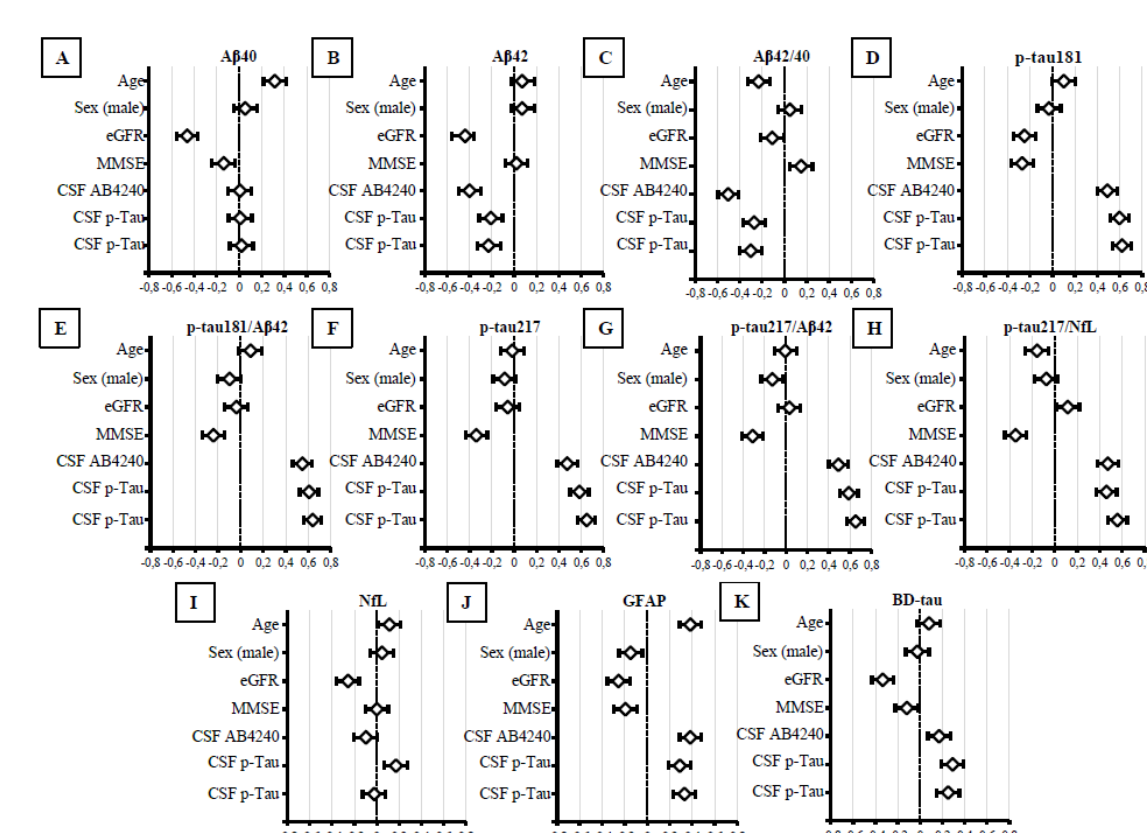


2- Correlation and regression analyses

Correlation analyses confirmed a significant inverse relationship between eGFR and most biomarkers. As illustrated, decreasing eGFR was associated with increasing concentrations of Aβ40, Aβ42, p-tau181, NfL, GFAP, and BD-tau in both amyloid-positive and amyloid-negative patients. These associations were statistically significant and consistent across subgroups. In contrast, no significant correlation was observed between eGFR and p-tau217 levels, highlighting its relative independence from renal function.



Similarly, no association was found for biomarker ratios such as p-tau217/Aβ42, NfL/p-tau217, and p-tau181/Aβ42. These findings were further supported by linear regression analyses, which demonstrated that eGFR remained significantly associated with most individual biomarkers even after adjustment for age. Importantly, this association disappeared when ratios were considered, confirming their robustness.



3- Stability of biomarker ratios

Unlike individual biomarkers, all evaluated ratios (Aβ42/Aβ40, p-tau217/Aβ42, NfL/p-tau217, and p-tau181/Aβ42) showed no significant differences across eGFR groups. Their distributions remained stable regardless of renal function, and no meaningful correlation with eGFR was detected. This suggests that the use of ratios effectively compensates for the systematic increase in biomarker concentrations induced by reduced renal clearance.

Blood Biomarker	eGFR<60 (n=36)	eGFR[60-90] (n=194)	eGFR>90 (n=190)	p-value ⁽¹⁾	η ² (1)	Aβ+ (n=243)	Aβ- (n=177)	p-value ⁽²⁾	η ² (2)	p-value ⁽²⁾	η ² (2)
p-tau217 (pg/mL)	0.63±0.64	0.39±0.35	0.38±0.41	**	0.028	0.59±0.43	0.16±0.24	***	0.257	*	0.012
Aβ42 (pg/mL)	45±10.1	35.4±7.5	32.5±7	***	0.17	32.3±7.2	38.4±8.3	***	0.132	*	0.011
Aβ40 (pg/mL)	362.1±69.5	304.2±48.3	279.9±43.2	***	0.183	301.4±50.2	293.7±57.1	ns	0.005	**	0.022
Aβ42/40 (%)	12.5±2	11.7±2.1	11.7±2.6	ns	0.01	10.7±1.7	13.2±2.2	***	0.282	*	0.011
p-tau217/Aβ42 (%)	1.5±1.6	1.3±1.4	1.3±1.4	ns	0.003	1.9±1.5	0.4±0.6	***	0.272	ns	0.004
NfL/p-tau217 (%)	1962±1778	2239±2563	2421±3059	ns	0.002	1133±1229	3897±3377	***	0.248	ns	0.002
p-tau181 (pg/mL)	1.9±1.1	1.3±0.7	1.1±0.7	***	0.085	1.6±0.8	0.9±0.4	***	0.240	ns	0.008
p-tau181/Aβ42 (%)	4.6±2.9	3.9±2.5	3.8±2.8	ns	0.006	5.2±2.8	2.3±1.2	***	0.286	ns	0.007
NfL (pg/mL)	6.1±4.5	4.4±2.5	3.7±3.1	***	0.047	4.1±2.1	4.3±4.1	ns	0.001	ns	0.007
GFAP (pg/mL)	175.8±77.4	143.7±60.8	117.3±58.3	***	0.079	158±58.7	102.3±55.8	***	0.186	*	0.011
BD-tau (pg/mL)	16±7.8	11.3±4.8	9.7±4.7	***	0.109	12±5.2	9.6±5.3	***	0.051	ns	0.004

4- Diagnostic performance for amyloidosis

The impact of renal function on diagnostic accuracy was particularly evident when analyzing individual biomarkers. As renal function declined, the specificity of several markers, including p-tau181, NfL, GFAP, BD-tau, and Aβ42/Aβ40—decreased significantly. This indicates an increased rate of false positives in patients with impaired kidney function. In contrast, p-tau217 showed stable diagnostic performance across all eGFR groups, with no significant variation in sensitivity or specificity. Among all tested markers, the p-tau217/Aβ42 ratio demonstrated the best overall performance. It achieved high sensitivity (approximately 0.89) and specificity (approximately 0.86) in the whole cohort, and these values remained consistent across all levels of renal function. Similarly, other ratios such as NfL/p-tau217 and p-tau181/Aβ42 maintained stable performance metrics.

Blood Biomarker	Threshold	WP		eGFR<60		eGFR [60-90]		eGFR>90		P-value	
		Se	Sp	Se	Sp	Se	Sp	Se	Sp	Se	Sp
p-tau217 (pg/mL)	0.22	0.84 [0.8-0.88]	0.88 [0.85-0.91]	0.96 [0.89-1.02]	0.92 [0.83-1]	0.83 [0.78-0.89]	0.83 [0.77-0.88]	0.82 [0.76-0.87]	0.93 [0.89-0.97]	ns	ns
Aβ42/40 (%)	11.6	0.77 [0.73-0.81]	0.79 [0.75-0.82]	0.54 [0.38-0.70]	0.75 [0.61-0.89]	0.77 [0.71-0.83]	0.76 [0.7-0.82]	0.83 [0.76-0.88]	0.81 [0.76-0.87]	ns	ns
p-tau217/Aβ42 (%)	0.54	0.89 [0.86-0.92]	0.86 [0.83-0.89]	1 [1-1]	0.92 [0.83-1]	0.89 [0.84-0.93]	0.8 [0.74-0.86]	0.87 [0.82-0.92]	0.89 [0.85-0.94]	ns	ns
NfL/p-tau217 (%)	6.19	0.83 [0.8-0.87]	0.85 [0.82-0.89]	0.88 [0.77-0.98]	1 [1-1]	0.83 [0.78-0.89]	0.84 [0.79-0.89]	0.82 [0.76-0.87]	0.85 [0.8-0.9]	ns	ns
p-tau181 (pg/mL)	1.03	0.83 [0.8-0.87]	0.76 [0.72-0.8]	0.92 [0.83-1]	0.42 [0.26-0.58]	0.83 [0.78-0.89]	0.69 [0.62-0.75]	0.81 [0.75-0.87]	0.88 [0.84-0.93]	ns	***
p-tau181/Aβ42 (%)	3.17	0.82 [0.79-0.86]	0.88 [0.84-0.91]	0.92 [0.83-1]	0.92 [0.83-1]	0.80 [0.74-0.85]	0.85 [0.8-0.9]	0.83 [0.77-0.88]	0.88 [0.84-0.93]	ns	ns
NfL (pg/mL)	2.48	0.89 [0.86-0.92]	0.35 [0.3-0.4]	0.96 [0.89-1]	0 [0-0]	0.88 [0.83-0.92]	0.18 [0.12-0.23]	0.89 [0.84-0.93]	0.56 [0.49-0.64]	ns	***
GFAP (pg/mL)	98.2	0.88 [0.85-0.91]	0.58 [0.53-0.63]	0.96 [0.89-1]	0.42 [0.26-0.58]	0.89 [0.85-0.94]	0.43 [0.36-0.49]	0.84 [0.79-0.89]	0.75 [0.69-0.81]	ns	***
BD-tau (pg/mL)	7.92	0.85 [0.82-0.89]	0.45 [0.4-0.5]	0.96 [0.89-1]	0.08 [0-0.17]	0.84 [0.79-0.89]	0.33 [0.26-0.4]	0.85 [0.8-0.9]	0.62 [0.55-0.69]	ns	***

Conclusion/Perspectives

• These findings confirm that renal function significantly influences circulating levels of neurodegeneration biomarkers, likely due to reduced renal clearance and possibly additional pathophysiological mechanisms linking kidney dysfunction and brain injury. The magnitude of this effect varies across biomarkers, with p-tau217 appearing less affected than others. Importantly, the use of biomarker ratios effectively mitigates this confounding effect, probably because both components of the ratio are similarly influenced by renal function.

• Renal function is a major confounding factor in the interpretation of blood biomarkers of neurodegeneration, leading to systematic overestimation of their concentrations. However, biomarker ratios, and particularly the p-tau217/Aβ42 ratio, remain robust and provide reliable diagnostic performance irrespective of kidney function. These results strongly support the preferential use of ratios in clinical practice, especially in populations with heterogeneous renal function.