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Blood-based biomarkers for Alzheimer's disease: influence of kidney function

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Abstract

Background Blood-based biomarkers are increasingly incorporated into the diagnostic work-up of Alzheimer's disease (AD). Systemic conditions such as kidney dysfunction (KD) may influence their plasma concentrations and complicate clinical interpretation. While the association between KD and blood AD biomarkers has been previously reported, practical strategies to mitigate this effect has not been defined. For these reasons, we evaluated the impact of KD on plasma levels of phosphorylated tau (p-Tau217, p-Tau181), amyloid-β (Aβ42/Aβ40), and neurofilament light chain (NfL), and developed correction strategies.

Methods We retrospectively selected 112 individuals (52 with AD, 21 with other neurodegenerative diseases, and 39 with non-neurodegenerative conditions) with available CSF AT biomarker profiles and paired plasma samples, all with documented abnormal renal function within one year from sampling. Plasma p-Tau217, p-Tau181, Aβ42/Aβ40, and NfL were measured on a fully automated chemiluminescent immunoassay platform (Lumipulse). Creatinine was re-measured on serum samples collected together with plasma samples to ensure temporal correspondence between kidney function and biomarker assessments. KD was defined as eGFR < 60 mL/min/1.73 m^2. We assessed the impact of KD on plasma biomarkers and evaluated correction strategies based on serum creatinine and eGFR, using CSF biomarkers as a biological reference.

Results KD was associated with higher plasma concentrations of p-Tau217, p-Tau181, Aβ42, Aβ40, and NfL, not with the Aβ42/Aβ40 ratio. Creatinine- and eGFR-based correction improved the correlation between plasma and CSF NfL. For AD classification, plasma p-Tau217 showed the highest diagnostic accuracy (AUC: 0.955, 95% CI: 0.920–0.990), with creatinine correction resulting in a numerical but not statistically significant improvement (AUC: 0.965, 95% CI 0.937–0.993), whereas a modest, not significant, increase in performance was observed for p-Tau181 after correction (AUC from 0.830, 95% CI: 0.752–0.907; to 0.862, 95% CI: 0.790–0.933). Corrected p-Tau cut-offs closely aligned with those previously reported in cohorts without KD.

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Conclusions KD alters plasma biomarker concentrations. Correction for renal function may be particularly relevant in individuals with moderate-severe KD and may facilitate the application of established plasma biomarker cut-offs derived from cohorts without KD.

Keywords Alzheimer's disease, Plasma, Biomarkers, Kidney, Renal dysfunction, p-Tau217, p-Tau181, NfL

Introduction

Fluid biomarkers improve the accuracy in the diagnosis of Alzheimer's disease (AD) [1–3]. The scalability, ease of collection, and patient acceptance of blood sampling make it a more viable option compared to lumbar puncture or nuclear medicine investigations [4]. Consequently, diagnostic algorithms are increasingly incorporating blood biomarkers into the diagnostic journey for suspected AD cases or when ruling out AD is necessary [5]. Whether blood biomarkers will serve as standalone indicators or as initial tests followed by further investigations remains a topic of debate, and both scenarios may be valid depending on individual cases [6]. In either situation, the reliability of blood biomarkers is of paramount importance.

Beyond diagnostic accuracy, which is notably high for certain biomarkers like tau phosphorylated at threonine 217 (p-Tau217) [7], and predictive values, which can vary significantly based on clinical context [6], blood biomarkers must reliably reflect brain pathology without being influenced by external systemic factors. Research has shown that systemic variables, such as body mass index, can affect plasma neurofilament light chain (NfL) levels [8], and certain comorbidities, like kidney dysfunction (KD), are associated with elevated concentrations of p-Tau217, tau phosphorylated at threonine 181 (p-Tau181), and NfL in plasma [9–13]. This effect is particularly pronounced for p-Tau181 and NfL, and less so for p-Tau217, which appears relatively resilient to systemic confounders, with KD becoming potentially relevant mainly in more severe cases where the need for a biomarker-based diagnosis may be less critical.

Given the potential for blood biomarkers to become widely used diagnostic tools, a thorough analysis of the impact of KD on their concentrations is essential. Moreover, strategies to adjust for these effects are necessary, but have not yet been adequately addressed. Importantly, while the association between KD and blood-based AD biomarkers has been previously reported, less attention has been paid to how this interaction should be handled in routine clinical practice. In particular, the availability of fully automated platforms suitable for large-scale implementation raises the question of whether simple, pragmatic correction strategies may help mitigate KD-related bias and facilitate the application of plasma biomarker cut-offs derived from cohorts without KD.

For this reason, we conducted this study with the following aims:

1. To assess the impact of KD on plasma concentrations of p-Tau217, p-Tau181, Aβ42/Aβ40 and NfL measured using chemiluminescent immunoassay (CLEIA) on the fully automated Lumipulse G1200 platform (Fujirebio), which is a candidate for widespread use in measuring blood biomarkers, in a cohort of patients with AD and other neurological diseases, all with available CSF AT(N) profiles.
2. To develop and evaluate correction strategies to mitigate the impact of KD on plasma biomarker concentrations, with CSF as a reference.

Methods

Study population

We retrospectively analyzed plasma samples of 112 patients consecutively referred to the Section of Neurology, University Hospital of Perugia, Italy, between January 2017 and December 2023.

All patients underwent medical history, physical and neurological examination, a thorough neuropsychological evaluation, brain imaging (computed tomography or magnetic resonance imaging), and lumbar puncture for the measurement of CSF core AD biomarkers, namely

Table 1 Demographical and clinical features

	AD	ND	OND
n	52	21	39
F/M	19/33	5/16	14/25
Age – yrs *mean ± SD*	76.2 ± 5.9	74.3 ± 6.4	74.5 ± 5.3
MMSE *mean ± SD*	20.7 ± 7	23.8 ± 3.7	25.9 ± 3.2
A-T- *n (%)*	0	17 (81)	23 (59)
A-T+ *n (%)*	0	3 (14.3)	12 (30.8)
A+T- *n (%)*	0	1 (4.7)	4 (10.2)
A+T+ *n (%)*	52 (100)	0	0
KD+ *n (%)*	29 (55.8)	7 (33.3)	22 (56.4)
Severe KD *n (%)*	1 (1.9)	0	4 (10.2)

Abbreviations. AD Alzheimer's disease. A+/- T+/-: combination of cerebrospinal fluid biomarkers with or without abnormal Aβ42/Aβ40 and with or without abnormal p-Tau181. KD+: individuals with kidney dysfunction, i.e. estimated glomerular filtration rate < 60 ml/min/1.73 m^2. MMSE: Mini Mental State Examination. *ND*: neurodegenerative diseases non-AD. *OND*: other neurological diseases. *Severe KD*: severe kidney dysfunction, i.e. estimated glomerular filtration rate < 30 ml/min/1.73 m^2

Aβ42/40, p-Tau181 and total tau (t-Tau). Patients were defined as A + or A- and as T + or T- based on previously calculated internal cut-off values of CSF Aβ42/40 and p-Tau181, measured with the use of the Lumipulse® G600 (Fujirebio, Japan) [14]. Specifically, A + status was defined by a CSF Aβ42/40 ratio < 0.072, whereas T + status was defined by CSF p-Tau181 concentrations > 50 pg/mL. For the purposes of this study, classification was based on biological A/T status rather than clinical stage. Accordingly, individuals with an A+/T + CSF profile were grouped together irrespective of cognitive status (cognitively unimpaired, mild cognitive impairment, or dementia).

The cohort included 52 patients with AD, defined by a CSF profile A+/T+, 21 patients with non-AD neurodegenerative diseases (ND), including Parkinson's disease

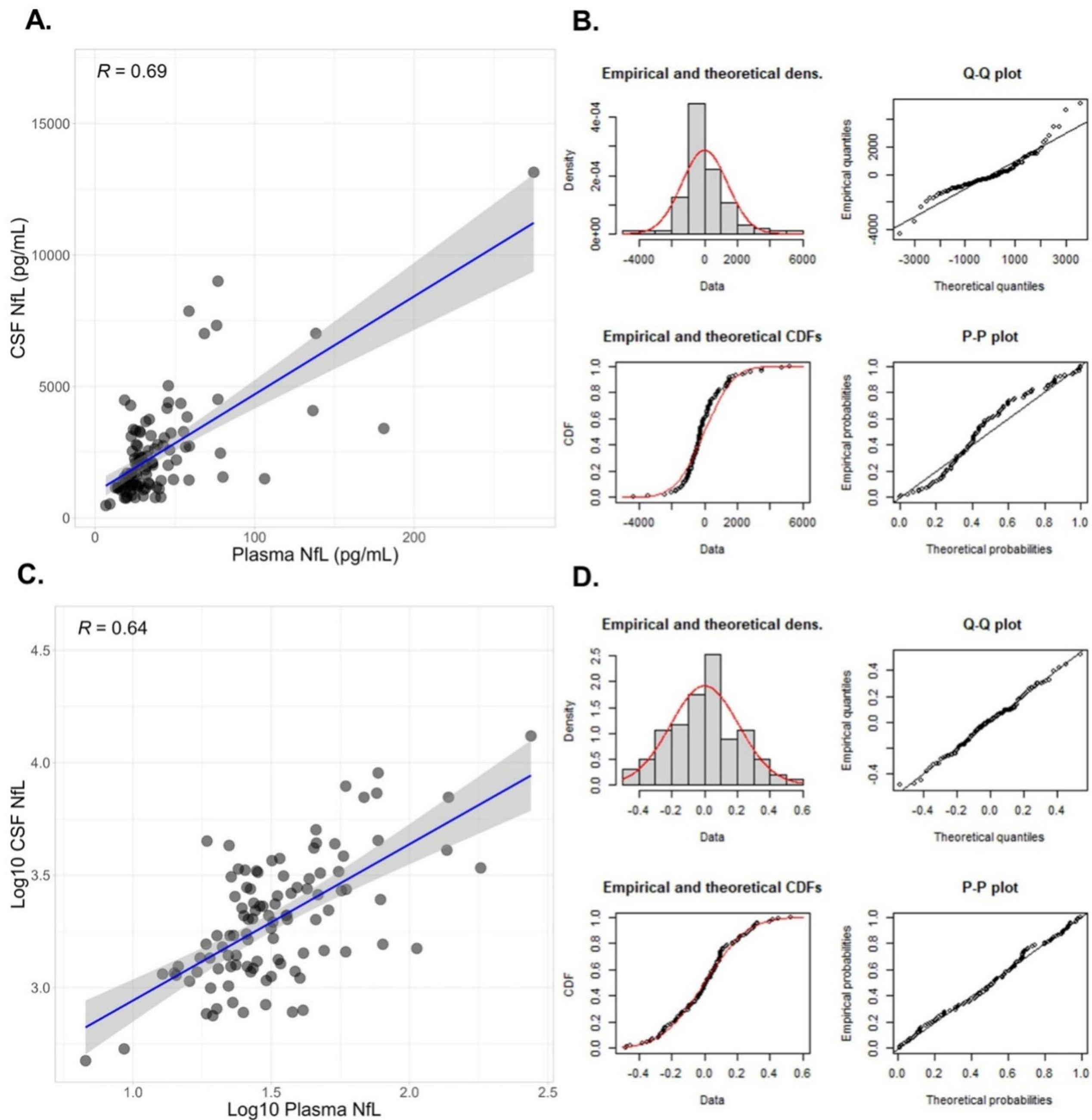

Fig. 1 Linear regression of CSF and plasma NfL. Panels show (**A**) Linear regression of CSF and plasma NfL; (**B**) Residual distribution analysis of raw CSF and plasma NfL; (**C**) Linear regression of Log10 CSF and plasma NfL; (**D**) Residual distribution analysis of Log10-trasformed data. Abbreviations. *CDFs*: cumulative density fractions. *CSF*: cerebrospinal fluid. *Dens.*: density. *NfL*: Neurofilament light chain. *P-P plot*: probability-probability plot. *Q-Q plot*: quartile-quartile plot

(PD) ($n = 6$), progressive supranuclear palsy (PSP) ($n = 6$), frontotemporal dementia (FTD) ($n = 5$), corticobasal syndrome (CBS) ($n = 2$), motor neuron disease (MND) ($n = 1$), and Huntington's disease (HD) ($n = 1$), with different CSF profiles (A+/T+, A+/T-, A-/T+, and A-/T-), and 39 individuals with non-neurodegenerative neurological diseases (OND), who underwent lumbar puncture as part of their diagnostic workup (Supplementary Table 1), with CSF profiles A+/T-, A-/T+, and A-/T- (Table 1).

Patients were selected for this study if they had one or more blood tests with an abnormal estimated glomerular filtration rate (eGFR) value within a year from lumbar puncture (eGFR < 60 mL/min/1.73 m²). Creatinine was re-measured on serum samples collected with plasma samples, and eGFR was re-calculated.

AD patients (n = 52) were diagnosed according to a CSF biomarker profile A+/T+, independent of the clinical stage, in line with the 2018 National Institute of Aging–Alzheimer's Association criteria [15]. PD, PSP, FTD, CBS,

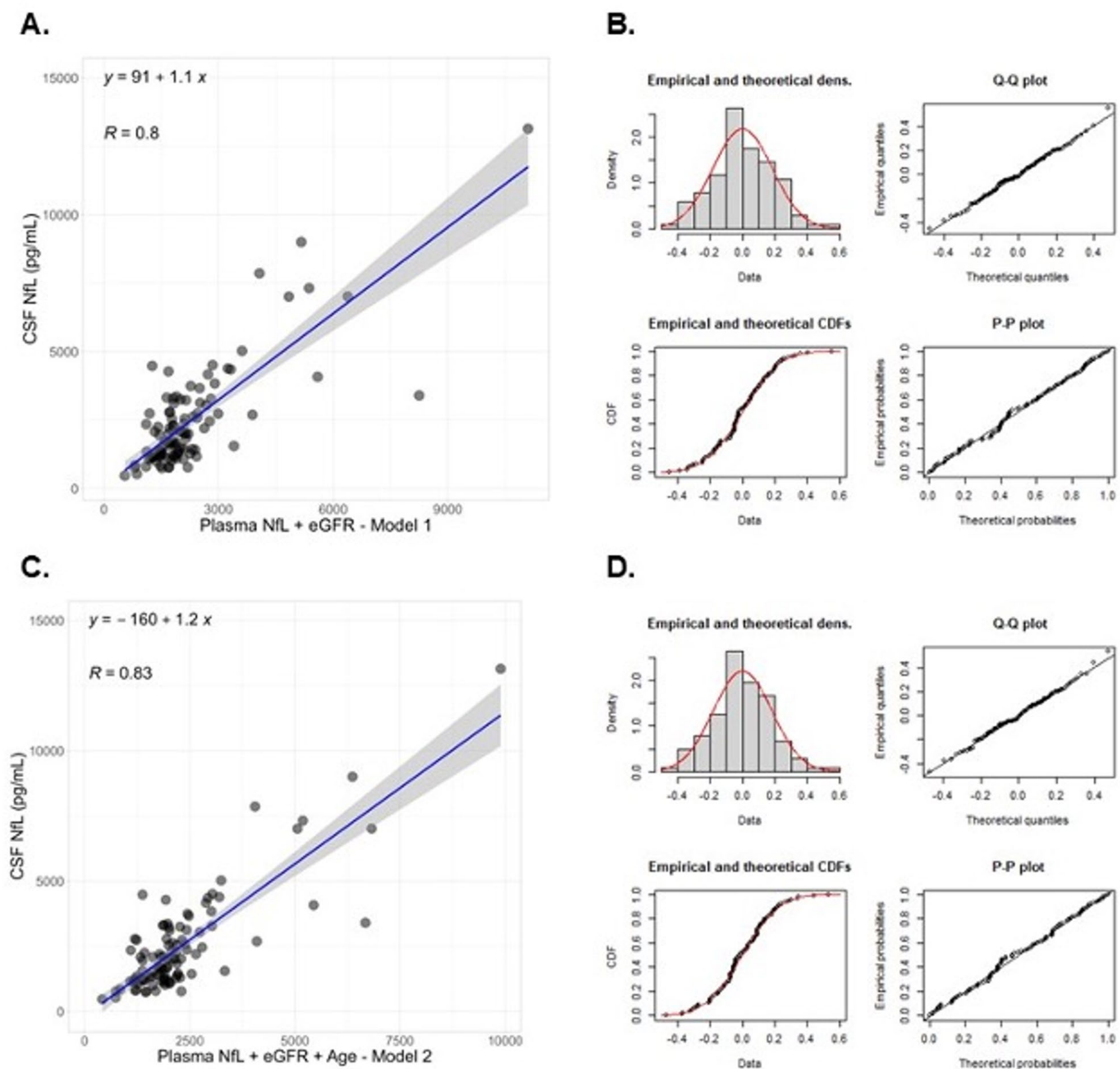

Fig. 2 Linear regression of CSF NfL and plasma NfL + eGFR (Model 1) and CSF NfL and plasma NfL + eGFR + age (Model 2). Panels show (**A**) Linear regression of CSF NfL and plasma NfL + eGFR (Model 1); (**B**) Residual distribution analysis of the Model 1; (**C**) Linear regression of CSF NfL and plasma NfL + eGFR + age (Model 2); (**D**) Residual distribution analysis of the Model 2. Abbreviations. *CDFs*: cumulative density fractions. *CSF*: cerebrospinal fluid. *Dens.*: density. *eGFR*: estimated glomerular filtration rate. *NfL*: Neurofilament light chain. *P-P plot*: probability-probability plot. *Q-Q plot*: quartile-quartile plot.

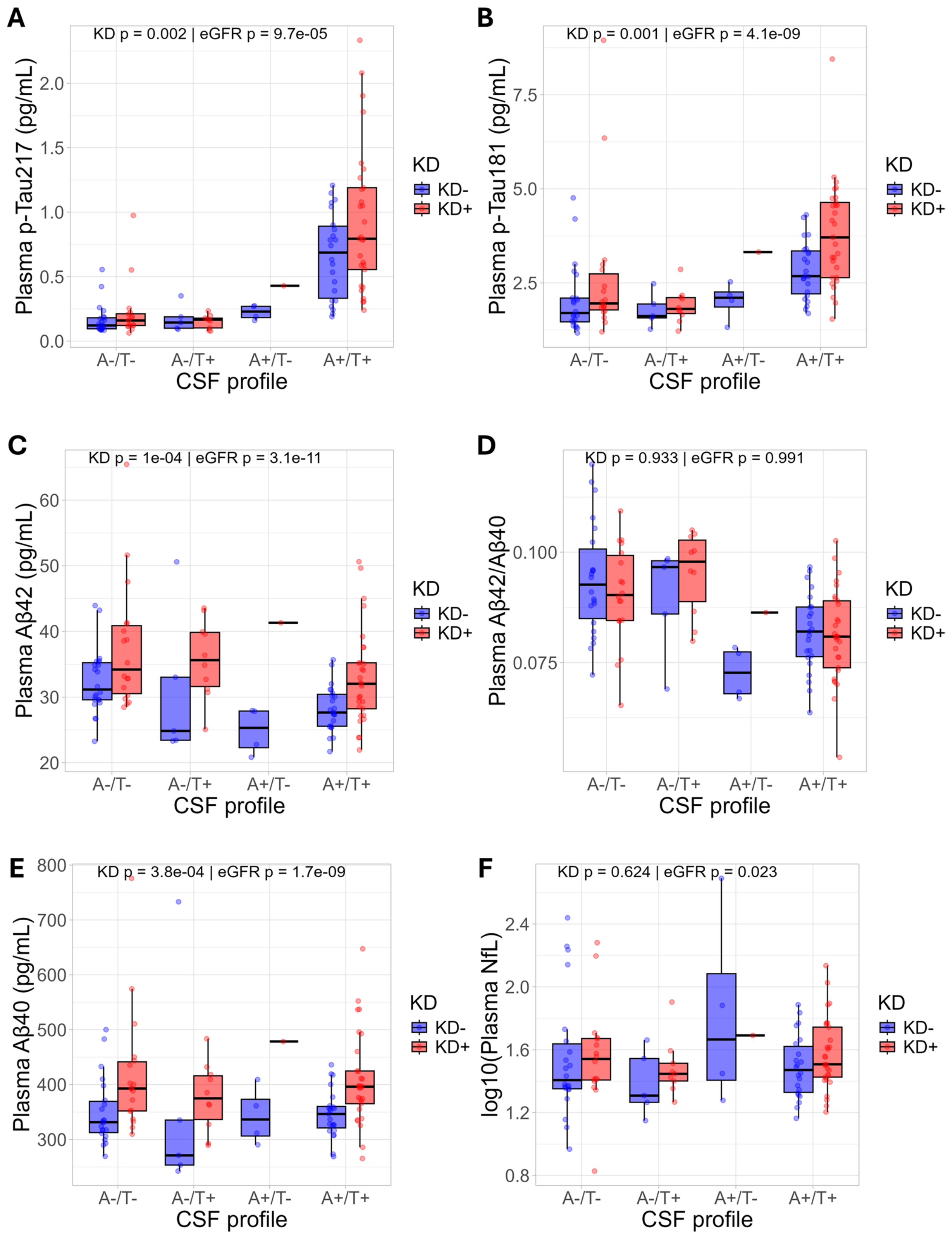

Fig. 3 (See legend on next page.)

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Fig. 3 Plasma AD biomarker concentrations in CSF A/T categories for subjects with and without KD. Panels **A**–**F** show plasma levels of p-Tau217, p-Tau181, Aβ42, Aβ42/Aβ40, Aβ40 and NfL, respectively, stratified by CSF A/T profile. Distributions are shown separately for individuals with (KD+) and without (KD–) kidney dysfunction. Boxplots represent the interquartile range, the horizontal line indicates the median, and whiskers extend to 1.5 times the interquartile range. The effect of kidney dysfunction (KD) was assessed using two-way ANOVA with CSF A/T status as a grouping factor, and by ANCOVA using estimated glomerular filtration rate (eGFR) as a continuous covariate. Abbreviations: KD+, kidney dysfunction (estimated glomerular filtration rate < 60 mL/min/1.73 m^2); KD–, no kidney dysfunction.

MND and HD patients (n = 21) were diagnosed according to the current diagnostic criteria [16–21].

The main demographic and clinical features of each diagnostic group are summarized in Table 1. Plasma biomarkers concentrations in each diagnostic group are reported in Supplementary Table 2.

Sample collection

All patients underwent lumbar puncture and venipuncture at the Section of Neurology, University Hospital of Perugia, Italy, and CSF and plasma were collected, handled, and stored according to international guidelines [22]. Collection of human CSF, serum and plasma samples has been performed following international guidelines and the same standard operating procedures (SOPs) throughout the study [22]. Lumbar puncture was performed between 8:00 a.m. and 10:00 a.m. CSF was collected into sterile polypropylene tubes and centrifuged for 10 min at 2000 × g at room temperature. At the same time, plasma was collected into sterile polypropylene tubes containing EDTA as the anticoagulant and centrifuged for 10 min at 2000 × g at room temperature. Serum tubes have micro silica particles attached to the inside that activate coagulation when the tubes are gently inverted after collection, they were also centrifuged for 10 min at 2000 × g at room temperature. Once processed, CSF, plasma and serum samples were stored in 0.5 mL tubes (72.730.007, Sarstedt, Germany) and immediately frozen at -80 °C pending analysis.

Results

Impact of renal function on the correlation between CSF and plasma NfL To assess the degree of correlation between CSF and plasma NfL, linear regression analysis was applied. Although the Pearson's correlation between raw CSF and plasma NfL concentrations was moderate to strong (Fig. 1 – A), the analysis of the residuals (Fig. 1 – B) prompted us to consider Log10-transformed data to meet the assumptions of linear regression (Fig. 1 – C). Indeed, applying linear regression on Log10-transformed data resulted in approximately normally distributed residuals (Fig. 1 – D), thus meeting the assumptions of linear regression.

Subsequently, eGFR, serum creatinine, plasma Aβ40, and age were incorporated with plasma NfL to predict CSF NfL concentration. The covariate showing the most significant contribution when added to plasma NfL was eGFR (p-value = $6.2*10^{-7}$) (Supplementary Table 3), and it was accordingly chosen as the primary correction factor. This first adjustment applied in Log10 space, referred to as "Model 1", resulted in an improved correlation (from the original $R = 0.69$ to $R = 0.8$, as shown in Fig. 2 – A) when considering back-transformed data. Indeed, after applying eGFR correction in Log10 space, back-transformed data met the assumptions of linear regression (Fig. 2 – B).

Next, the impact of introducing a second covariate was evaluated. Only age showed significant association (p-value = 0.01) (Supplementary Table 4) and was therefore chosen as an additional adjustment factor to be included. This adjustment, referred to as "Model 2", resulted in a marginally improved correlation (from the initial $R = 0.8$ to $R = 0.83$ in linear space, depicted in Figure 2 – C). Indeed, after applying eGFR + age correction in Log10 space, back-transformed data met the assumptions of linear regression (Figure 2 – D). The value of the coefficients and the standard error of the variables used in Model 2 are reported in Supplementary Table 5.

Impact of renal function on plasma AD biomarkers and biomarker ratios

Concerning all other plasma biomarkers of AD considered, through a two-way ANOVA and ANCOVA analyses, it was revealed that KD and eGFR exert a pronounced effect on plasma p-Tau217, p-Tau181, and Aβ42 but not on plasma Aβ42/Aβ40, as shown in Fig. 3A – D. By accounting for CSF A/T profile, plasma levels of p-Tau217, p-Tau181, and Aβ42 were higher in KD + than in KD- patients (by two-way ANOVA) and found associated to eGFR (by ANCOVA). The results for Aβ40 and NfL are shown for completeness in Fig. 4E – F. However, the interpretation of group-based analyses requires caution. Although both biomarkers are influenced by kidney function, they are not specific markers of AD. Accordingly, stratification according to CSF status may have limited biological relevance.

When considering biomarker ratios, the influence of KD on plasma levels of p-Tau217/Aβ42 (p-value KD = 0.06), p-Tau217/Aβ40 (p-value KD = 0.065), p-Tau181/Aβ42 (p-value KD = 0.172), p-Tau181/Aβ40 (p-value KD = 0.192) was less evident (Fig. 4A – D). However, p-Tau181/Aβ42 and p-Tau181/Aβ40 were not significantly affected by KD according to two-way ANOVA but was still affected by eGFR as indicated by ANCOVA

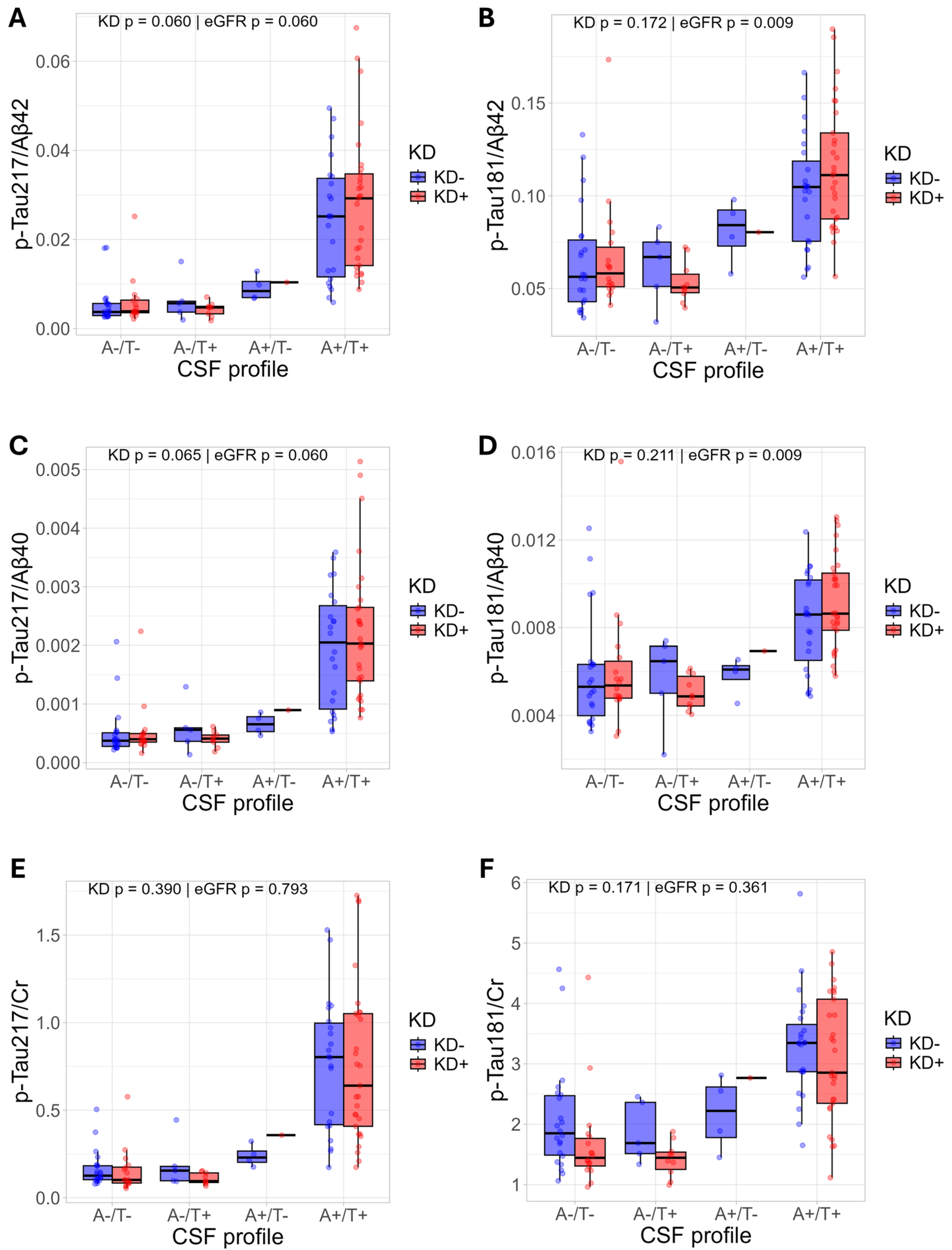

Fig. 4 (See legend on next page.)

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Fig. 4 Plasma AD biomarker ratios in CSF A/T categories for subjects with and without KD. Panels show (**A**-**B**) Plasma levels of p-Tau181/Aβ42 and p-Tau217/Aβ42 grouped for the A/T profile of KD+ and KD- subjects; (**C**-**D**) Plasma levels of p-Tau181/Aβ40 and p-Tau217/Aβ40 grouped for the A/T profile of KD+ and KD- subjects; (**E**-**F**) Plasma levels of p-Tau181/creatinine and p-Tau217/creatinine grouped for the A/T profile of KD+ and KD- subjects. Plasma biomarkers ratio in KD- and KD+ subjects are displayed as boxplots in which the boxes represent the interquartile range, the horizontal lines within boxes represent the median concentrations and whiskers reflect the first/third quartile ± 1.5 times the interquartile range. The effect of kidney dysfunction (KD) was assessed using two-way ANOVA with CSF A/T status as a grouping factor, and by ANCOVA using estimated glomerular filtration rate (eGFR) as a continuous covariate. Abbreviations. KD+: subjects with kidney dysfunction (estimated glomerular filtration rate < 60 ml/min/1.73 m^2). KD-: subjects without kidney dysfunction (estimated glomerular filtration rate ≥ 60 ml/min/1.73 m^2)

(p-value eGFR = 0.009). In contrast, p-Tau217/Aβ42 and p-Tau217/Aβ40 ratio were not significantly affected by eGFR (p-value ANCOVA eGFR = 0.06), although the association almost reached the statistical significance.

Conversely, the impact of KD was significantly minimized by the p-Tau217/creatinine ratio (p-value 2-way-ANOVA KD = 0.39, p-value ANCOVA eGFR = 0.79) and the p-Tau181/creatinine ratio (p-value 2-way-ANOVA KD = 0.17, p-value ANCOVA eGFR = 0.36) (Fig. 4E – F). Following these results, and the well-known sex-dependance of serum creatinine values, it was decided to normalize p-Tau values with creatinine values adjusted to the mean values by sex [24].

Impact of creatinine, Aβ40, and Aβ42 corrections on plasma p-Tau217 and p-Tau181 accuracy

A ROC analysis was performed to evaluate the accuracy of p-Tau217 and p-Tau181 using serum creatinine and sex correction (p-Tau217corr. and p-Tau18 corr.), ratio on Aβ40, and ratio on Aβ42 in predicting an A + T + CSF profile. The following parameters were evaluated: threshold, accuracy, sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV) and Youden. Cut-offs (threshold) are shown based on two levels of sensitivity and specificity restriction (95% and 90%) and the best accuracy obtained for each analyte (Table 2) (Supplementary Fig. 1). For p-Tau217corr. and p-Tau181corr., ROC curves and distributions are displayed in Figs. 5 and 6, respectively. Across all analyses, p-Tau217 consistently showed the highest diagnostic performance for AD, both before and after correction, confirming its role as the most robust plasma biomarker of AD among those evaluated. Uncorrected plasma p-Tau217 yielded an AUC of 0.955 (95% CI 0.920–0.990), with creatinine- and sex-corrected p-Tau217 showing a numerically similar performance with AUC of 0.965 (95% CI 0.937–0.993) (Fig. 5), without a statistically significant difference between corrected and uncorrected measures according to DeLong testing.

For plasma p-Tau181, diagnostic accuracy was overall lower compared with p-Tau217. Uncorrected p-Tau181 showed an AUC of 0.830 (95% CI 0.752–0.907), while creatinine- and sex-corrected p-Tau181 resulted in a modest numerical increase in performance with AUC of 0.862 (95% CI 0.790–0.933) (Fig. 5). Even in this case, the difference between corrected and uncorrected p-Tau181 did not reach statistical significance.

Renal function correction formulas for plasma NfL, p-Tau217 and p-Tau181

The ready-to-apply corrections are reported below:

$$CSF\ NfL_{Model\ 1} = eGFR^{0.9} * plasma\ NfL^{0.77} * 10^{0.54} \quad (1)$$

$$CSF\ NfL_{Model\ 2} = eGFR^{0.94} * plasma\ NfL^{0.72} * age^{1.45} * 10^{-2.16} \quad (2)$$

$$\text{Plasma pTau}_{\text{corr}} = \text{s} * 0.9 * \frac{\text{pTau}}{\text{Cr}} + 0.7 * (1-\text{s}) * \frac{\text{pTau}}{\text{Cr}} \quad (3)$$

The first Eq. (1) represents the result of the log-linear regression of CSF NfL vs. NfL and eGFR, referred to as "Model 1". The second Eq. (2) represents the log-linear regression of CSF NfL vs. NfL, eGFR and age, referred to as "Model 2". The third Eq. (3) represents the correction for plasma p-Tau, both p-Tau217 and p-Tau181 (s = 1 for males, s = 0 for females, Cr = serum creatinine concentration).

Discussion

In this study, we evaluated the impact of KD on plasma concentrations of AD biomarkers (p-Tau217, p-Tau181, Aβ42, Aβ40, and NfL), with the aim of proposing correction models to reduce this effect. Our results confirm that KD increases plasma levels of these biomarkers, leading to higher concentrations in individuals with impaired renal function. For the first time, we also explore pragmatic, ready-to-apply correction strategies aimed at mitigating this effect in selected clinical scenarios. Several previous studies have demonstrated an association between KD and increased plasma concentrations of AD-related biomarkers, including p-Tau217, p-Tau181, and NfL, using different analytical platforms and study designs [9, 25, 26]. Most of these works have primarily focused on describing the magnitude of this association or on adjusting statistical models for renal function as a covariate. In contrast, the present study builds on this evidence by addressing a more translational question: whether kidney-related bias can be mitigated in a pragmatic manner that is compatible with routine clinical use. By combining a fully automated immunoassay platform with paired CSF A/T biomarker profiling as a biological

Table 2 Cut-off, accuracy, sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV) and Youden evaluated for plasma p-Tau217 and p-Tau181, plasma p-Tau217 and p-Tau181 corrected for creatinine and sex, p-Tau217/Aβ40, p-Tau181/Aβ40, p-Tau217/Aβ42, p-Tau181/Aβ42, and Aβ42/Aβ40 for the CSF A+/T+vs. other comparison

Plasma p-Tau217, AUC = 0.955							
Scenario	**Cut-off (pg/mL)**	**Accuracy**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Youden**
95% sens	0.238	89%	96%	82%	0.83%	0.96%	1.79
90% sens	0.268	88%	90%	86%	85%	91%	1.76
Best accuracy	0.290	90%	90%	89%	88%	91%	1.80
90% spec	0.405	84%	76%	91%	89%	81%	1.68
95% spec	0.554	83%	67%	96%	95%	77%	1.65
Plasma p-Tau181, AUC = 0.830							
Scenario	**Cut-off (pg/mL)**	**Accuracy**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Youden**
95% sens	1.790	68%	96%	43%	59%	93%	1.39
90% sens	1.985	71%	90%	55%	64%	87%	1.45
Best accuracy	2.330	78%	81%	75%	74%	82%	1.56
90% spec	3.065	74%	56%	90%	83%	70%	1.46
95% spec	4.220	63%	27%	95%	82%	60%	1.22
Plasma p-Tau217 corrected for creatinine and sex, AUC = 0.965							
Scenario	**Cut-off (pg/mL)**	**Accuracy**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Youden**
95% sens	0.186	89%	96%	82%	83%	96%	1.79
Best accuracy	0.229	91%	92%	89%	89%	93%	1.82
90% sens	0.236	90%	90%	89%	88%	91%	1.80
90% spec	0.246	88%	86%	89%	88%	88%	1.76
95% spec	0.337	85%	73%	96%	95%	80%	1.69
Plasma p-Tau181 corrected for creatinine and sex, AUC = 0.862							
Scenario	**Cut-off (pg/mL)**	**Accuracy**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Youden**
95% sens	1.483	77%	94%	62%	68%	93%	1.56
90% sens ssensens	1.581	78%	90%	67%	70%	89%	1.57
Best accuracy	1.950	81%	77%	85%	82%	81%	1.62
90% spec	2.351	74%	56%	90%	83%	70%	1.46
95% spec	2.945	63%	25%	95%	81%	59%	1.20
Plasma p-Tau217/Aβ40, AUC = 0.956							
Scenario	**Cut-off**	**Accuracy**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Youden**
95% sens	0.007	90%	96%	84%	84%	96%	1.80
Best accuracy	0.007	90%	96%	84%	84%	96%	1.80
90% sens	0.008	89%	90%	88%	87%	91%	1.78
90% spec	0.009	89%	86%	91%	90%	88%	1.77
95% spec	0.015	82%	67%	96%	94%	76%	1.63
Plasma p-Tau181/Aβ40, AUC = 0.853							
Scenario	**Cut-off**	**Accuracy**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Youden**
95% sens	0.050	67%	96%	45%	60%	93%	1.41
90% sens	0.058	73%	90%	65%	65%	88%	1.49
Best accuracy	0.067	82%	83%	82%	80%	84%	1.64
90% spec	0.083	76%	60%	90%	84%	72%	1.50
95% spec	0.098	70%	40%	95%	88%	65%	1.35
Plasma p-Tau217/Aβ42, AUC = 0.959							
Scenario	**Cut-off**	**Accuracy**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Youden**
95% sens	0.082	91%	96%	86%	86%	96%	1.82
Best accuracy	0.082	91%	96%	86%	86%	96%	1.82
90% sens	0.096	88%	90%	86%	85%	91%	1.76
90% spec	0.109	89%	86%	91%	90%	88%	1.78
95% spec	0.181	81%	65%	96%	94%	75%	1.61

Table 2 (continued)

Plasma p-Tau181/Aβ42, AUC = 0.884

Scenario	Cut-off	Accuracy	Sensitivity	Specificity	PPV	NPV	Youden
95% sens	0.060	74%	96%	55%	65%	94%	1.51
90% sens	0.071	79%	90%	68%	71%	89%	1.59
Best accuracy	0.080	83%	83%	83%	81%	85%	1.66
90% spec	0.097	79%	65%	90%	85%	75%	1.55
95% spec	0.110	71%	42%	95%	88%	65%	1.37

Plasma Aβ42/Aβ40, AUC = 0.780

Scenario	Cut-off	Accuracy	Sensitivity	Specificity	PPV	NPV	Youden
95% sens	0.097	65%	95%	35%	60%	86%	1.29
Best accuracy	0.094	69%	90%	47%	64%	81%	1.37
90% sens	0.084	71%	65%	78%	46%	68%	1.43
90% spec	0.078	65%	40%	91%	82%	60%	1.31
95% spec	0.073	57%	21%	95%	80%	54%	1.16

Abbreviations. *AUC* area under the curve. *CSF* cerebrospinal fluid. *NPV* negative predictive value. *PPV* positive predictive value. *Sens*: sensitivity. *Spec.*: specificity

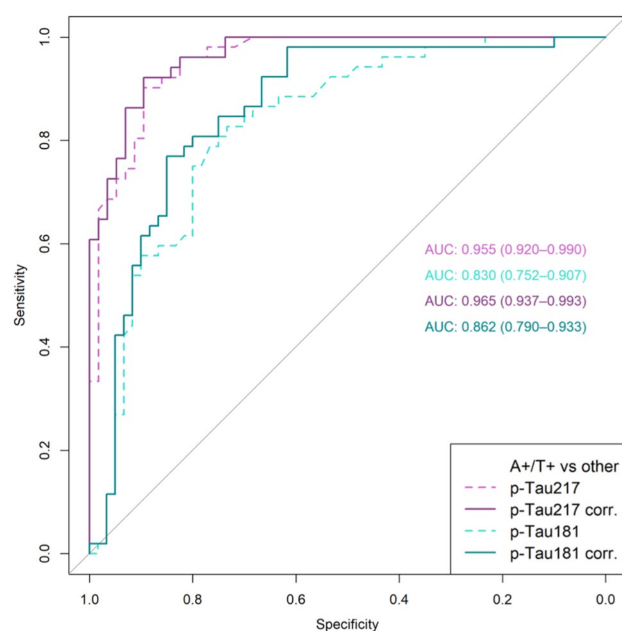

Fig. 5 ROC curves assessing the ability of plasma p-Tau181 and p-Tau217, both alone and corrected for serum creatinine and sex, to differentiate between the CSF A+T+ profile and the non-A+T+ profile. AUC values with 95% confidence intervals are shown for each comparison. Abbreviations. *AUC* area under the ROC curve. *Corr*: corrected for serum creatinine and sex. *CSF*: cerebrospinal fluid

reference, our approach moves beyond descriptive associations and explores how renal correction may support the application of plasma biomarker cut-offs derived in cohorts without KD. In this study, different analytical approaches were applied according to the biological properties of each biomarker. For NfL, plasma–CSF correlation was used as the primary endpoint, given the well-established quantitative relationship between compartments. In contrast, plasma–CSF correlations for p-tau isoforms are known to be moderate [23], and a CSF equivalent of p-tau217 is not available on the same platform. Therefore, p-tau biomarkers were evaluated in relation to CSF-defined AD status rather than through direct plasma–CSF correlation, which better reflects their intended clinical use.

As previously shown [23, 27], the effect on Aβ42 can be easily compensated by using the Aβ42/Aβ40 ratio. We therefore tested whether Aβ40 or Aβ42 could also normalize the concentrations of other plasma biomarkers. For p-Tau217 and p-Tau181, the ratio with Aβ40 and Aβ42 reduced the impact of KD. For plasma NfL, nor plasma Aβ40 nor plasma Aβ42 improved the association with CSF NfL.

Aβ40 and Aβ42 share a similar metabolic pathway, systemic catabolism, and are likely filtered by the kidneys in the same way [28]. Aβ40 can be considered a reliable proxy for total Aβ levels, and Aβ42/40 ratio adjusts for inter-individual differences in Aβ production [29]. This relationship does not necessarily extend to other biomarkers with different molecular weights, which may undergo different renal processing. Thus, while Aβ40 is suitable to normalize Aβ42, its use for other plasma biomarkers is questionable.

For plasma p-Tau217 and p-Tau181, the best normalization for renal function was obtained by using the ratio with creatinine. After correcting for creatinine and sex, no differences were found in plasma p-Tau217 and p-Tau181 between AD patients with and without KD and no residual association with eGFR was present. Based on these results, we developed a formula to adjust plasma p-Tau levels for KD when present.

Among the plasma biomarkers examined, p-Tau217 emerged as the primary reference marker, showing the highest diagnostic accuracy for AD, and the greatest resilience to renal-related confounding. Compared to raw plasma values, creatinine-corrected p-Tau217 and p-Tau181 showed slightly higher accuracy in

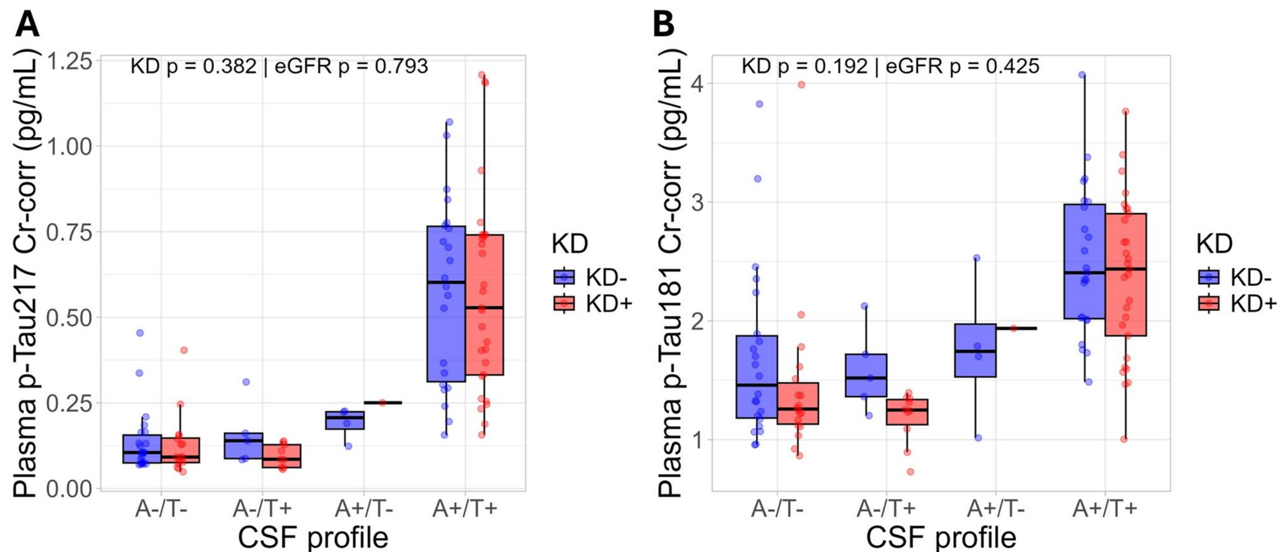

Fig. 6 Plasma p-Tau corrections for serum creatinine in CSF A/T categories for subjects with and without KD. Panels show (**A**) Plasma levels of p-Tau217 corrected for creatinine and grouped to A/T profile of KD+ and KD- subjects; (**B**) Plasma levels of p-Tau181 corrected for creatinine and grouped to A/T profile of KD+ and KD- subjects. Plasma biomarkers in KD- and KD+ subjects are displayed as boxplots in which the boxes represent the interquartile range, the horizontal lines within boxes represent the median concentrations and whiskers reflect the first/third quartile ± 1.5 times the interquartile range The effect of kidney dysfunction (KD) was assessed using two-way ANOVA with CSF A/T status as a grouping factor, and by ANCOVA using estimated glomerular filtration rate (eGFR) as a continuous covariate. Abbreviations. KD+: subjects with kidney dysfunction (estimated glomerular filtration rate < 60 ml/min/1.73 m^2). KD-: subjects without kidney dysfunction (estimated glomerular filtration rate ≥ 60 ml/min/1.73 m^2)

distinguishing AD from non-AD cases, although this difference was not statistically significant. Previous studies have shown that KD affects p-Tau217 levels, but the effect is smaller than the impact of being A+ [27]. In our study, the incremental diagnostic gain obtained through correction was modest for p-Tau217, whose performance remained high even without adjustment. This finding supports the concept that routine correction of p-Tau217 for renal function is unlikely to be necessary in most clinical settings, and that adjustment may be primarily relevant in individuals with moderate to severe KD. This reinforces the suitability of plasma p-Tau217 as a blood-based diagnostic marker of AD.

In this cohort enriched in patients with KD (50%), creatinine adjustment allowed us to obtain cut-off values (listed in Table 2) closer and more consistent with those reported by Arranz et al. [27], and Bellomo et al., [23], which were measured in independent cohorts with small numbers of KD patients (less than 5%). This suggests that renal correction may be particularly useful to support the transferability of established cut-offs to populations with impaired renal function, rather than to substantially increase diagnostic accuracy per se. For NfL, the variables most strongly influencing the correlation between plasma and CSF concentrations were eGFR and age. This led to a formula (Model 2) that improved the plasma–CSF correlation. Adjusting plasma NfL for age and eGFR may therefore increase the reliability of peripheral NfL measurements.

AD biomarkers differ from many other laboratory measures commonly influenced by renal function. Biomarkers such as p-Tau217 are increasingly considered candidate standalone diagnostic markers of AD, a role that has been explicitly recognized in recent diagnostic frameworks [30]. In this context, plasma biomarkers may directly inform etiological diagnosis, eligibility for disease-modifying therapies, and long-term therapeutic monitoring, all of which carry substantial clinical, economic, and ethical implications [31–33]. For these reasons, diagnostic accuracy and biological specificity are particularly critical, and even modest systematic biases related to comorbid conditions may translate into clinically meaningful misclassification. The aim of renal correction is therefore not to mandate universal adjustment, but rather to reduce the risk of false-positive interpretation in selected individuals, especially those with moderate to severe KD, and to support the use of cut-offs derived from highly selected cohorts largely free of renal comorbidity.

A strength of our study is the use of an automated immunoassay platform, which ensures highly reproducible and standardized results, minimizes pre-analytical and analytical variability, and is cost-effective and scalable [34]. Further, individuals with an A+/T + CSF profile were grouped irrespective of clinical stage. This approach was intentionally adopted to prioritize biological characterization over clinical staging. This choice reflects the growing use of plasma biomarkers, particularly

p-Tau217, as tools for biological diagnosis rather than for staging disease progression. A limitation is the current unavailability of the p-Tau217 assay in CSF, which prevents assessing its plasma-CSF correlation and potential adjustment for other variables. In addition, kidney function may vary over time, and this temporal variability may influence the application of renal correction strategies. Accordingly, any correction should ideally be performed using renal function parameters measured contemporaneously with plasma biomarker assessment, rather than relying on retrospective values. Although in our study serum creatinine was re-measured at the time of plasma sampling in the present study, residual variability may still introduce noise into correction models. Therefore, the proposed formulas should be interpreted as cross-sectional adjustments and validated in prospective cohorts. Furthermore, although we accounted for renal function, other systemic factors such as body mass index and liver function were not considered and should be explored in future studies.

Conclusion

Our findings may have clinically relevant implications. Given the increasing use of plasma biomarkers in AD diagnosis and in clinical trials, correction for renal function may be considered in selected cases, particularly in individuals with moderate to severe KD, to allow reliable application of cut-offs generated on cohorts unaffected by KD. Moreover, validation in independent larger cohorts and prospective studies will be crucial to confirm the generalizability of these correction strategies.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13195-026-01970-4.

Supplementary Material 1.

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Role of funders

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the research article.

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Authors' contributions

LG, GB, DC, and LP contributed to the conception and design of the work. LG, GB, GN, AToj, CS, EG, EGT, FPP, AV, and AToz contributed to the acquisition, analysis and interpretation of data.LG, GB, DC, GN, AToj, and CS drafted the manuscript.LG, GB, AToz, DC, and LP substantially revised the manuscript. All the authors approved the submitted version of the manuscript and agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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Data availability

Anonymized data not published within this article will be made available by request from any qualified investigator.

Declarations

Competing interests

L. Gaetani has participated in advisory boards for and received writing or speaker honoraria and travel grants from Almirall, Biogen, Eisai, Euroimmun, Fujirebio, Lilly, Merck, Mylan, Novartis, Roche, Sanofi, Siemens Healthineers, and Teva. G. Bellomo received honoraria from Fujirebio and completed paid consultancies for Parkinson's Foundation. He received travel/educational grants from Fujirebio and Alzheimer's Association. D. Chiasserini has nothing to disclose. L. Parnetti served as Member of Advisory Boards for Fujirebio, IBL, Roche, and Merck.

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