Journal of Clinical Laboratory Analysis

WILEY

RESEARCH ARTICLE OPEN ACCESS

Evaluation of Soluble Triggering Receptor Expressed on Myeloid Cells 2 (sTREM2) in Cerebrospinal Fluid, Serum, and Plasma Using the Fully Automated Lumipulse Platform

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Received: 24 November 2025 | **Revised:** 21 January 2026 | **Accepted:** 23 March 2026

Keywords: Alzheimer's disease | automated immunoassay | biomarkers | blood | cerebrospinal fluid | Lumipulse platform | microglia

ABSTRACT

Background: In this study, we first evaluated the relationship between sTREM2 concentrations in CSF, serum, and plasma of Alzheimer's disease (AD) patients using the newly developed Lumipulse G sTREM2 assay.

Methods: sTREM2 was measured by the fully automated Lumipulse G1200 platform (Fujirebio). Associations and agreement between matrices were assessed using Passing–Bablok regression, Spearman correlation, and Bland–Altman analyses. Subanalyses explored the influence of disease stage and tau pathology.

Results: Median sTREM2 concentrations were highest in CSF, followed by serum and plasma. Serum and CSF sTREM2 levels showed a moderate but significant correlation ($\rho = 0.32$; $p = 0.0012$), although regression analysis indicated poor linearity. In contrast, serum and plasma sTREM2 levels were strongly correlated ($\rho = 0.74$; $p < 0.001$). The association between CSF and serum sTREM2 levels was independent of total and phosphorylated tau. Notably, a strong CSF–serum correlation was observed in the MCI due to AD group ($\rho = 0.74$) but was completely lost in overt AD dementia, demonstrating a clear disease stage–dependent relationship.

Conclusion: CSF and blood sTREM2 capture partly distinct biological processes and show limited overall agreement. While serum and plasma sTREM2 are closely related, they are not interchangeable.

1 | Introduction

Alzheimer's disease (AD), the leading cause of dementia worldwide, is marked by the accumulation of amyloid-beta plaques and tau tangles in the brain [1, 2]. Although these pathological hallmarks have been the focus of extensive research, the complex mechanisms driving AD remain poorly understood, hindering the development of effective treatments. Recently, attention has shifted toward the role of neuroinflammation and the brain's innate immune response, particularly involving microglia, the resident immune cells of the central nervous system.

Microglia play a crucial role in maintaining brain homeostasis by clearing debris, supporting synaptic function, and

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responding to injury [3]. In AD, they become activated around amyloid plaques, exhibiting either protective or harmful phenotypes depending on the disease stage and environment [4]. A key regulator of microglial activity is Triggering Receptor Expressed on Myeloid Cells 2 (TREM2), a receptor that, through its signalling partner DAP12, promotes microglial survival, proliferation, and phagocytosis [5]. Importantly, mutations in the TREM2 gene, such as R47H, significantly increase the risk of developing late-onset AD by impairing its protective functions [6]. This evidence further supports the role of TREM2 in AD pathology.

A soluble form of this receptor, namely soluble TREM2 (sTREM2), generated by proteolytic cleavage of the extracellular domain of membrane-bound TREM2, is released into the cerebrospinal fluid (CSF) [7]. Interestingly, CSF sTREM2 levels fluctuate throughout the course of AD, typically rising during early symptomatic stages and declining as the disease progresses [8–15].

Elevated CSF sTREM2 has been reported in AD patients as early as 12–14 years before the onset of clinical symptoms [16]. These early increases are thought to reflect microglial activation in response to amyloid deposition and neuronal injury, underscoring the role of neuroinflammation in the initial phases of AD [8]. In cognitively normal individuals with evidence of amyloid pathology, sTREM2 levels are often reduced. However, as the disease progresses to the MCI and early dementia stages, sTREM2 levels increase, suggesting a compensatory microglial response to increasing neurodegeneration. Thus, sTREM2 may serve as a predictor of disease progression [16, 17].

Longitudinal studies in autosomal-dominant AD further support this evidence. Indeed, increased rates of sTREM2 elevation in CSF are associated with slower cortical atrophy and reduced cognitive decline, suggesting a protective microglial response during disease progression [18, 19]. Beyond its predictive value, sTREM2 may thus also provide prognostic information [19].

Taken together, these findings highlight a biphasic pattern, in which sTREM2 reflects distinct phases of microglial activation across AD stages. Mechanistically, sTREM2 supports microglial survival and proliferation, stimulates cytokine production, and promotes clustering around amyloid plaques, facilitating their clearance [20]. In animal models, increased sTREM2 levels mitigate amyloid pathology and improve cognitive outcomes, whereas genetic variants that impair sTREM2 function increase AD risk and compromise microglial responses [6, 21–23].

Overall, sTREM2 captures neuroinflammatory activity and microglial engagement in AD pathogenesis. It complements established biomarkers, offering additional value for diagnosis, prognosis, and therapeutic monitoring. Although robust evidence supports the role of sTREM2 in CSF as a biomarker of AD, only a few Authors explored the value of blood sTREM2 [24, 25]. Nonetheless, the non-invasive nature of blood-based testing makes blood sTREM2 an attractive candidate for screening and longitudinal monitoring, provided that future studies can standardize measurements and clarify its relationship with central nervous system pathology.

Recently, Fujirebio developed an assay for measuring sTREM2 in plasma and serum on Lumipulse, which is a fully automated platform widely adopted in clinical neurochemistry laboratories worldwide.

In this study, we first evaluated the correlation between CSF, serum, and plasma levels of sTREM2 measured by this new assay.

2 | Materials and Methods

2.1 | Study Population

This is a retrospective observational study performed at the Policlinico "Paolo Giaccone", University of Palermo, Italy. We included 102 AD patients at different stages of disease who underwent lumbar puncture for CSF collection as a part of the routine clinical diagnostic work-up. The diagnosis of AD was made according to the current criteria. Specifically, all patients underwent a complete medical and neurological evaluation, complete routine blood measurement, neuropsychological evaluation, brain magnetic resonance imaging (MRI), fluorodeoxyglucose (FDG)-positron emission tomography (PET), and CSF withdrawal as routine diagnostic procedures. All AD patients showed brain atrophy in MRI scans, brain hypometabolism at FDG-PET, and AD core CSF biomarkers abnormalities. All patients were amyloid positive. CSF was obtained by a lumbar puncture at the L3/4 or L4/5 interspace using a 21-gauge needle. It was collected in polypropylene tubes, centrifuged at 500 g for 20 min, aliquoted in polypropylene tubes, and stored at −80°C until analysis.

For each patient, we also collected whole blood sample in a dry tube and a K_3-EDTA tube to obtain serum and plasma, respectively, after centrifugation for 10 min at 2.500 g at room temperature. The serum and plasma were collected, aliquoted into 500 μL portions in polypropylene tubes, and immediately stored at −80°C until analysis, avoiding repeated freeze–thaw cycles. All patients signed informed consent. The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Policlinico P. Giaccone Palermo.

2.2 | Laboratory Analysis

Serum, plasma, and CSF sTREM2 levels were measured using the Lumipulse G sTREM2 assay on the fully automated platform Lumipulse G1200 (FUJIREBIO Inc., Tokyo, Japan), according to the manufacturer's instructions.

The assay is based on the standard Lumipulse G two-step sandwich immunoassay principle used for other neurodegeneration biomarkers. Briefly, a biotinylated anti-sTREM2 antibody and an antibody-coated particle capture reagent are incubated with the specimen to form a solid-phase immune complex; after washing, alkaline-phosphatase–labelled streptavidin (or conjugate antibody, depending on assay design) is added, followed by a chemiluminescent substrate (AMPPD). The light signal at ~477 nm generated by alkaline-phosphatase–mediated dephosphorylation of AMPPD

is measured by the analyser and is directly proportional to the sTREM2 concentration in the sample.

The limit of detection is 2.1 pg/mL for CSF, 2.0 pg/mL for serum, and 1.6 pg/mL for plasma; the limit of quantification (at 20% CV) is 2.7 pg/mL for CSF, 2.2 pg/mL for serum, and 2.4 pg/mL for plasma, and the precision of less than 5% coefficient of variation (CV). The intra-assay CV is < 5%. Controls and calibrators were run in duplicates, and the mean of the duplicate values was used as the final readout. All samples were in a single run, using a single lot of reagents. No dilution of the sample was required. For CSF samples, the reported concentration needs to be multiplied by 1.33 to obtain the neat sTREM2 concentration in CSF, as recommended by the manufacturer.

2.3 | Statistical Analysis

The relationship between CSF and serum measurements was assessed using Passing–Bablok regression, a non-parametric method robust to outliers and measurement error in both variables. The regression equation, slope, and intercept were estimated with 95% confidence intervals obtained by bootstrap resampling (quantile method). Monotonic association was further evaluated using Spearman's rank correlation coefficient (ρ).

Residual analysis was performed on the Passing–Bablok regression fit to inspect the distribution of deviations across the measurement range and assess potential heteroscedasticity.

Agreement between the matrices was evaluated with the Bland–Altman method. Mean differences and limits of agreement (mean±1.96 SD) were calculated both on the absolute scale and after logarithmic transformation, the latter allowing assessment of proportional differences expressed as ratios. For each plot, the mean bias and 95% limits of agreement were reported.

All statistical analyses were performed in R (version 4.5.1; R Foundation for Statistical Computing, Vienna, Austria), using the mcr package version 1.3.3.1. A two-sided p-value < 0.05 was considered statistically significant.

3 | Results

In this study, we included 102 AD patients (57% MCI due to AD and 43% mild AD), median age of 67 years, and 54% females. Median concentration of sTREM2 was 2247 pg/mL in serum, 2107.8 pg/mL in plasma, and 4061.5 pg/mL in CSF, documenting that CSF has the highest levels, as expected.

Passing–Bablok regression between CSF and serum measurements ($n = 102$) yielded the following equation:

Serum sTREM2 = 1255.70 + 0.21 × CSF sTREM2.

With a Spearman correlation coefficient of ρ = 0.316 ($p = 0.0013$). Residuals ranged between −2000 and + 4000 without evidence of marked heteroscedasticity. Although moderately correlated, the regression fit is poor, with substantial scatter around the regression line. Hence, the model does not fully capture the relationship between serum and CSF concentration (Figure 1).

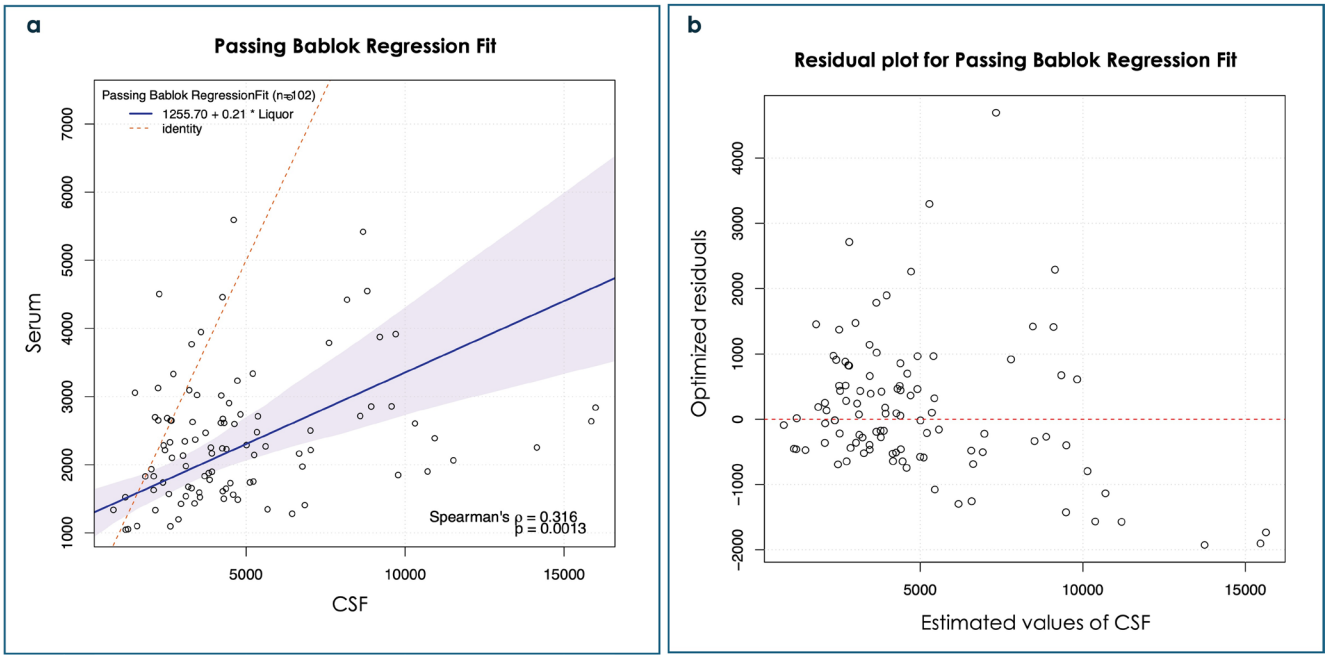

FIGURE 1 | Passing–Bablok regression analysis of serum and CSF sTREM2 levels. (a) Passing–Bablok regression plot showing the relationship between CSF (x-axis) and serum (y-axis) concentrations. The solid blue line represents the regression fit, with the shaded area indicating the confidence interval. The dashed line denotes the line of identity. Spearman's correlation coefficient (ρ) and p-value are reported. (b) Residual plot of the Passing–Bablok regression, showing optimized residuals plotted against estimated CSF values. The dashed horizontal line indicates zero residuals, used to assess systematic deviation and heteroscedasticity.

Bland–Altman analysis showed a mean difference of −2406.06, with limits of agreement between −8301.48 and + 3489.37. Analysis of the ratio indicated a mean ratio of 0.55, with limits of agreement from 0.18 to 1.71 (Figure 2). Overall, the analyses indicate wide variability between CSF and serum concentrations, with proportional differences observed. These findings suggest limited agreement between the two biological matrices.

In a subset of patients ($n = 30$), we explored the relationship between serum and plasma. A strong correlation was observed between sTREM2 levels in serum and plasma ($\rho = 0.7419$; $p < 0.001$) (Figure 3). Nonetheless, serum concentrations tended to be slightly higher than plasma concentrations, suggesting that these two biological matrices, while related, should not be used interchangeably.

We verified whether the CSF concentrations of phosphorylated Tau (pTau) and total Tau (tTau) could influence the association between CSF and serum concentrations of sTREM2. To verify if the serum-CSF association was merely a reflection of tau-related neurodegeneration, we performed a partial correlation analysis. The association between CSF and serum sTREM2 remained even after controlling for core AD biomarkers (adjusting for t-tau: $r = 0.53$, $p = 0.002$; adjusting for p-tau: $r = 0.51$, $p = 0.003$). These results indicate that the relationship between the CSF and serum is not a simple byproduct of tau pathology but represents an independent biological relationship.

We further explored this association by stratifying the cohort based on the median tTau levels (452 pg/mL). The correlation in the high-Tau group ($r = 0.51$, $p = 0.05$) was apparently stronger than the low-Tau group ($r = 0.38$, $p = 0.15$). However, the Fisher test revealed no significant difference between the correlations of the two groups ($p = 0.68$). Altogether, these findings suggest that the association between serum and CSF sTREM2 is apparently independent from tau levels.

After categorizing the cohort into MCI and overt AD, we observed a significant correlation in the MCI group ($\rho = 0.74$, $p = 0.002$), while the association was lost in the overt AD group ($\rho = 0.02$, $p = 0.96$). A formal comparison of these two correlation coefficients using Fisher's r-to-z transformation confirmed that the association is significantly stronger in the MCI stage compared to the AD stage ($p = 0.04$).

4 | Discussion

In this study, we investigated the relationship between sTREM2 concentrations in CSF, serum, and plasma measured using the newly developed Lumipulse G sTREM2 assay for the fully automated Lumipulse G1200 platform in a well-characterized cohort of AD patients at different clinical stages. Our main findings can be summarized as follows: (i) CSF sTREM2 concentrations were markedly higher than peripheral levels, as expected; (ii) CSF and serum sTREM2 levels showed only a modest correlation with poor agreement and wide inter-individual variability; (iii) serum and plasma sTREM2 levels were strongly correlated, although not interchangeable; and (iv) the association between CSF and serum sTREM2 was stage dependent, being evident in the MCI due to AD group but lost in overt AD.

The weak correlation between CSF and serum sTREM2 aligns with emerging evidence that blood-based and CSF biomarkers

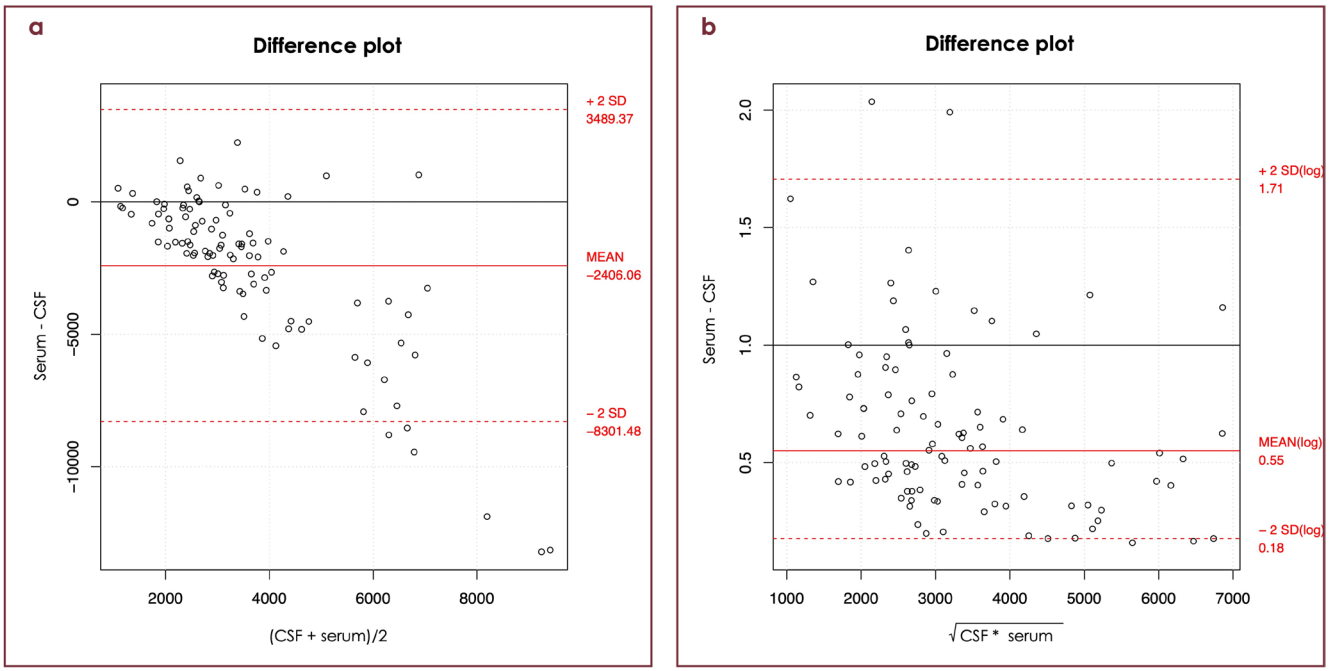

FIGURE 2 | Figure 2. Bland–Altman difference plots comparing serum and CSF sTREM2 levels. (a) Difference plot showing the absolute difference (serum − CSF) against the mean of serum and CSF values. The red solid line represents the mean difference (bias), while the dashed lines indicate the limits of agreement (±2 standard deviations). (b) Difference plot after logarithmic transformation, showing the ratio scale (log-transformed data) plotted against the geometric mean ($\sqrt{[\text{CSF} \times \text{serum}]}$). The red solid line indicates the mean log difference, and the dashed lines represent the limits of agreement (±2 standard deviations).

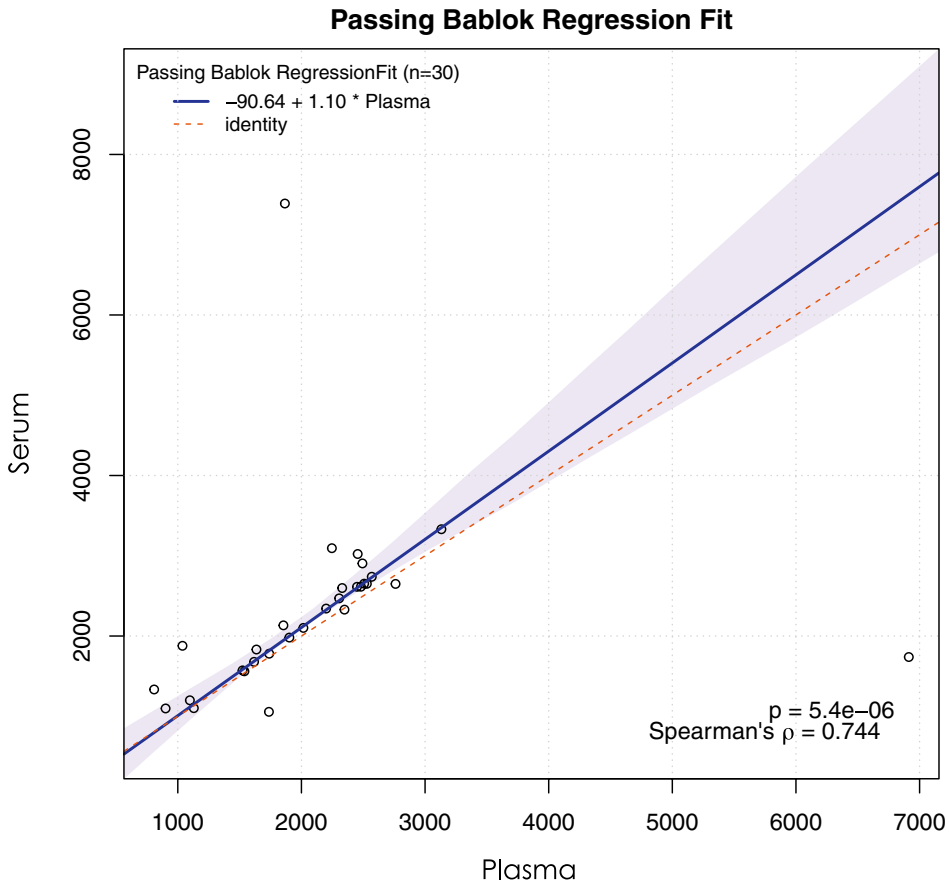

FIGURE 3 | Passing–Bablok regression analysis of plasma and serum sTREM2 levels. Passing–Bablok regression plot showing the relationship between plasma (x-axis) and serum (y-axis) concentrations. The solid blue line represents the regression fit, with the shaded area indicating the confidence interval, whereas the dashed line denotes the line of identity. Spearman's correlation coefficient (ρ) and *p*-value are reported.

may reflect distinct biological processes in neurodegenerative diseases [26, 27]. While CSF sTREM2 is generated primarily through proteolytic cleavage of membrane-bound TREM2 on activated microglia within the CNS, the sources of peripheral sTREM2 remain less well characterized [9, 28]. Peripheral myeloid cells, including monocytes and macrophages, also express TREM2 and may contribute to circulating sTREM2 levels [28, 29]. This dual origin could explain the limited concordance between compartments, as CSF sTREM2 predominantly reflects CNS microglial activity, whereas serum sTREM2 may represent a composite signal from both central and peripheral immune activation.

Although blood sTREM2 may not directly serve as a surrogate biomarker for CSF sTREM2, it could still provide valuable insights in AD. We are now entering the era of blood-based biomarkers for AD, driven by their practical advantages in terms of accessibility, scalability, and patient compliance compared with CSF and imaging markers. Additionally, the use of fully automated platforms such as Lumipulse further strengthens the potential clinical applicability of blood sTREM2 by enabling standardized, high-throughput testing. To date, only Ohara et al. and Yasuno et al. explored the value of serum sTREM2 in AD patients [24, 30]. They performed a prospective cohort study (2002–2012) involving 1349 Japanese community-dwelling individuals, aged 60 or older, initially free of dementia [30]. Participants were followed for 10 years for incident dementia, AD, and vascular dementia (VaD). The Authors found that incidence rates for all-cause dementia, AD, and VaD significantly increased across rising serum sTREM2 quartiles. Thus, they concluded that increased serum sTREM2 levels were associated with an increased risk of developing all-cause dementia, AD, and vascular dementia in the general elderly Japanese population. Yasuno et al. showed that higher serum sTREM2 levels, together with MCP-1, sex, and diagnostic category, reliably predict the degree of glial activation, as measured by in vivo PET imaging of TSPO in key brain regions [24]. This finding is particularly compelling because it suggests that blood-based sTREM2 may serve as a promising noninvasive biomarker for neuroinflammation in AD, potentially enabling earlier detection, monitoring of disease progression, and evaluation of treatment responses. Notably, serum levels of sTREM2 were measured by enzyme-linked immunosorbent assay (ELISA) in both studies. ELISA was the first technique used to measure blood sTREM2. However, its inherent disadvantages, such as labour-intensive procedures, variability between assays, and limited scalability, may have constrained the consistency and breadth of research in this area. These limitations could partly explain why the role of serum sTREM2 as a biomarker of neuroinflammation has not been fully clarified. However, the emergence of fully automated assay platforms capable of measuring sTREM2 with higher precision, reproducibility, and throughput represents a significant advance. Such technology opens new

opportunities to systematically investigate the diagnostic and prognostic value of serum sTREM2 across large cohorts, ultimately bringing this biomarker closer to clinical application.

The observation that serum concentrations were systematically higher than plasma concentrations is consistent with previous reports for other neurological biomarkers [31]. This difference likely reflects protein release during the clotting process in serum preparation. For tau and amyloid-β, studies have demonstrated that these proteins can be lost or altered during clot formation, resulting in lower serum concentrations compared to plasma [31]. The current findings suggest that sTREM2 may exhibit the opposite pattern, with potential release from platelets or other blood cells during coagulation. This underscores the importance of standardizing sample type for sTREM2 measurements, as serum and plasma values are not interchangeable despite their strong correlation [32, 33].

The independence of the CSF-serum sTREM2 association from tau pathology, as demonstrated by partial correlation analyses controlling for t-tau and p-tau, suggests that this relationship is not merely a reflection of neurodegeneration severity. This finding is particularly relevant given that CSF sTREM2 levels correlate strongly with tau biomarkers in cross-sectional studies [8, 9, 28]. The persistent association after adjusting for tau markers indicates that sTREM2 may capture distinct aspects of neuroinflammatory processes that are partially independent of tangle pathology.

The most striking finding is the disease stage-dependent divergence in CSF-serum correlation, with a significant association in MCI ($\rho = 0.74$) that was completely lost in overt AD ($\rho = 0.02$). This stage-specific pattern may reflect fundamental changes in the relationship between central and peripheral immune compartments as AD progresses. Several mechanisms could account for this observation. First, blood–brain barrier (BBB) integrity progressively deteriorates during AD progression [34–36]. While our data did not show a direct relationship between sTREM2 and albumin quotient, BBB dysfunction may still influence the bidirectional exchange of sTREM2 between CSF and blood in complex, non-linear ways that vary across disease stages [34, 37]. Second, the biphasic pattern of microglial activation across the AD continuum may contribute to this stage-dependent dissociation [38, 39]. Longitudinal PET studies have demonstrated that microglial activation peaks during the MCI stage and subsequently declines in established dementia [39]. During early disease stages, when microglia are actively responding to amyloid pathology, CSF sTREM2 levels rise and may correlate with peripheral immune activation. However, as disease progresses and microglia transition from a protective to a dysfunctional, pro-inflammatory phenotype, the coupling between central and peripheral TREM2 biology may be disrupted [40, 41]. This transition could explain why the CSF-serum correlation is preserved in MCI but lost in dementia. Third, the progressive accumulation of AD pathology may alter CSF dynamics and protein clearance mechanisms. Recent evidence suggests that impaired CSF clearance contributes to biomarker accumulation in the CNS, independent of BBB permeability [37]. As disease advances, reduced CSF turnover and impaired glymphatic drainage could diminish the exchange of sTREM2 between brain and blood compartments, decoupling CSF and serum measurements.

The clinical implications of these findings are significant for the development of blood-based sTREM2 as a biomarker. Although CSF sTREM2 has demonstrated robust utility for tracking neuroinflammation and predicting disease progression in AD, the current results suggest that serum sTREM2 may not serve as a reliable surrogate for CSF levels, particularly in later disease stages. This limitation is critical for clinical applications, as blood-based biomarkers are most valuable for screening and longitudinal monitoring in diverse populations [27, 42] The stage-dependent dissociation between compartments indicates that serum sTREM2 may have differential utility across the AD spectrum, potentially serving as a more informative biomarker during prodromal stages when the CSF-blood correlation is preserved.

The strong correlation between serum and plasma sTREM2 observed in our subset analysis provides practical guidance for assay implementation. While both matrices are viable, the systematic difference in absolute concentrations necessitates matrix-specific reference ranges and precludes direct comparison of values obtained from different sample types [32, 33]. This is consistent with recommendations for other blood-based AD biomarkers, where plasma is generally preferred due to more standardized collection procedures and reduced variability from clotting factors [42].

Several limitations warrant consideration. First, the cross-sectional design limits our ability to assess longitudinal changes in the CSF-serum relationship as individuals progress through disease stages. Longitudinal studies tracking both compartments over time would provide more definitive evidence regarding the temporal dynamics of this association. Another limitation is the absence of a cognitively healthy control group, particularly for cerebrospinal fluid analyses. The inclusion of such cohorts would be highly valuable for establishing reference ranges for sTREM2 and for further improving the standardization and comparability of measurements across analytical platforms. However, the availability of cerebrospinal fluid samples from cognitively normal individuals is limited due to ethical and practical constraints. Future studies incorporating well-characterized healthy control populations will be essential to address these gaps and to support the broader clinical implementation of sTREM2 as a biomarker. Future studies should therefore focus on defining reference intervals in healthy populations and on evaluating the clinical utility of blood sTREM2 as a biomarker for diagnosis, prognosis, and monitoring in AD. Another limitation of this study is the lack of a systematic assessment of frailty. Previous evidence indicates that sTREM2 concentrations may be influenced not only by age and sex but also by frailty-related factors [43]. As frailty was not evaluated in the present cohort, its potential contribution to variability in sTREM2 levels could not be addressed and may represent a confounding factor in the observed associations. Future studies incorporating standardized measures of frailty will be important to better account for these effects and to refine the interpretation of sTREM2 as a biomarker in Alzheimer's disease.

Finally, we did not assess peripheral inflammatory biomarkers or perform detailed phenotyping of circulating myeloid cells, which could provide mechanistic insights into the sources of serum sTREM2. Fourth, the study included only AD patients

without comparison to other neurodegenerative diseases, limiting our understanding of disease specificity.

Future research should address several key questions. Longitudinal studies examining paired CSF and blood samples across the AD continuum are needed to definitively establish how the relationship between compartments evolves with disease progression. Investigation of peripheral immune cell TREM2 expression and its contribution to serum sTREM2 would clarify the biological origins of blood-based measurements. The studies incorporating BBB integrity markers, CSF flow dynamics, and glymphatic function could elucidate mechanisms underlying the stage-dependent dissociation. Finally, validation of these findings in independent cohorts, including cognitively normal individuals with preclinical AD pathology, would establish whether the patterns observed here generalize across the full disease spectrum.

In conclusion, this study demonstrates that CSF and serum sTREM2 show limited agreement, with a disease stage-dependent relationship that is preserved in MCI but lost in overt AD dementia. While serum and plasma measurements correlate strongly, they are not interchangeable due to systematic concentration differences. These findings suggest that blood-based sTREM2 may not reliably reflect CNS microglial activity, particularly in advanced disease stages, limiting its utility as a surrogate for CSF measurements. The stage-specific patterns observed here highlight the complexity of biomarker relationships across biological compartments and underscore the need for careful validation of blood-based markers across the full AD spectrum. Future studies should focus on elucidating the mechanisms underlying compartment-specific sTREM2 dynamics and determining the optimal clinical applications for blood-based sTREM2 measurements in AD diagnosis and monitoring.

Acknowledgments

Open access publishing facilitated by Universita degli Studi di Palermo, as part of the Wiley - CRUI-CARE agreement.

Funding

The authors have nothing to report.

Ethics Statement

The study was approved by the Institutional Review Board of Policlinico P. Giaccone Palermo.

Consent

All patients signed informed consent.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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