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Heterogeneity of GFAP Expression in Alzheimer's Disease: A Perspective from the Vascular-Inflammation Axis

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Abstract: ***Based on the "vascular-inflammation axis" analytical framework, this study evaluates the pathophysiological significance of plasma glial fibrillary acidic protein (GFAP) in Alzheimer's disease (AD). We systematically analyze its expression heterogeneity and clinical interpretive boundaries, specifically comparing late-onset AD (LOAD) and early-onset AD (EOAD).***

Keywords: Alzheimer's disease, Glial fibrillary acidic protein, Blood biomarkers, Astrocytes, Cerebral small vessel disease, East Asian population.

1. Introduction

The diagnostic paradigm for Alzheimer's disease (AD) is undergoing a historic evolution from a "clinical syndrome definition" to a "biological definition." The updated 2024 diagnostic and staging framework by the Alzheimer's Association Workgroup further emphasizes the central role of amyloid-β (Aβ), tau protein, and neurodegeneration markers in disease stratification [1]. Against this backdrop, blood-based biomarkers have emerged as a focal point of research due to their low invasiveness, high reproducibility for longitudinal monitoring, and proximity to real-world clinical applications. Unlike traditional pathology-anchored markers (such as p-tau species), the unique clinical value and inherent limitations of glial fibrillary acidic protein (GFAP) both stem from its profound sensitivity to the pathological background, vascular comorbidities, and glial reactive states. Consequently, GFAP does not primarily answer "whether AD pathology is present"; rather, it is more suited for deciphering the heterogeneity manifested under specific pathological and comorbid contexts. It serves as a crucial entry point for discussing the heterogeneous expression of AD and the interpretive boundaries of mixed pathologies.

However, the biological interpretation of GFAP and its clinical extrapolability still face significant challenges. In late-onset AD (LOAD) and the AD continuum, the correlation between GFAP and Aβ pathology, cognitive decline, and brain atrophy has been repeatedly corroborated by multiple studies [2-4]; supplementary studies published post-search further suggest that dynamic changes in GFAP may correlate with subsequent cognitive decline and clinical progression, though this signal requires more prospective validation [5]. In contrast, in early-onset AD (EOAD)—especially sporadic EOAD—the expression patterns of related fluid biomarkers and their relationships with neuroimaging and clinical phenotypes still exhibit substantial heterogeneity. Current evidence in this area remains relatively limited and lacks consensus [6,7]. Recent evidence indicates that GFAP primarily acts as a fluid biomarker reflecting astrocyte reactivity within the AD continuum [8], implying that it predominantly mirrors the glial response to pathological processes rather than acting as a specific indicator of a single pathological pathway.

These phenomena suggest that reducing GFAP to a simple "linear readout of neuroinflammatory intensity" is clearly insufficient. As the roles of blood-brain barrier (BBB) breakdown, intercellular crosstalk within the neurovascular unit, microglia-mediated inflammatory cascades, and vascular brain injury in AD receive increasing recognition, GFAP can be viewed as a comprehensive response signal driven by the synergistic effects of Aβ pathology, tau propagation, cerebral small vessel disease (CSVD), and BBB dysfunction [9-13].

Building upon this, the present review utilizes the "vascular-inflammation axis" as an integrative perspective to delineate the evidence of GFAP heterogeneity across LOAD, EOAD, and autosomal dominant AD (ADAD). We focus specifically on three testable questions: first, whether CSVD burden systematically modulates the pathological implications of GFAP; second, whether this association remains robust after adjusting for age, sex, APOE ε4 status, and major vascular risk factors; and third, whether there is supporting temporal evidence linking GFAP longitudinal changes to disease progression. This review aims to explicitly define the boundaries of GFAP as a 'pathophysiological indicator' rather than a mere 'diagnostic biomarker', thereby mitigating the risk of circular reasoning in clinical translation.

2. Materials and Methods

To ensure methodological transparency and rigor, this study employed a structured literature search strategy integrated with a problem-driven evidence synthesis model. Although our approach was informed by the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) framework to maintain high standards of reproducibility, this work is presented as a structured narrative review. This categorization allows for a rigorous synthesis of existing data while maintaining the interpretive flexibility required to propose and evaluate the 'vascular-inflammation axis' framework [14]. Consequently, protocol pre-registration and quantitative meta-analysis were not conducted. All stages of the review—including title/abstract screening, full-text eligibility assessment, data

extraction, and quality appraisal—were performed independently by two researchers. Any discrepancies were resolved through consensus or, where necessary, adjudication by a third senior researcher. Methodological quality was assessed using the Newcastle-Ottawa Scale (NOS), while the primary evidence chain was graded according to the Oxford Centre for Evidence-Based Medicine (OCEBM) 2011 framework.

A systematic search was executed across PubMed, Embase, the Cochrane Library, China National Knowledge Infrastructure (CNKI), and Wanfang Data from inception through December 31, 2024. To maintain the timeliness of the 'vascular-inflammation axis' framework, several landmark studies published in early 2025 were also qualitatively incorporated to provide updated context, although the formal OCEBM evidence grading was strictly applied to the systematic search results [15].

Eligibility criteria were defined as: (1) original human studies quantifying the association between plasma GFAP and Alzheimer's disease pathology (Aβ/tau), cognitive trajectories, brain atrophy, or cerebral small vessel disease (CSVD) imaging markers; (2) studies providing longitudinal data, pathological anchoring, or specific data on East Asian cohorts; and (3) peer-reviewed publications. We prioritized original research over reviews to form the core evidence chain. Exclusion criteria included case reports, conference abstracts, unpublished dissertations, studies relying solely on cerebrospinal fluid (CSF) metrics, animal or in vitro models, and duplicate datasets (retaining only the most comprehensive report).

The screening process followed a structured workflow: an initial pool of 4,856 records was identified. After duplicate removal, 3,212 unique titles/abstracts were screened, leading to 186 full-text evaluations. Ultimately, 28 high-quality original studies that directly addressed our pre-defined research questions regarding GFAP heterogeneity and vascular-inflammatory overlap were included in the primary evidence chain. The remaining literature provided methodological support for quality appraisal [16].

3. Biological Basis and the "Vascular - Inflammation Axis"

Glial fibrillary acidic protein (GFAP) is an essential component of type III intermediate filament proteins in astrocytes. Its elevated expression typically indicates cytoskeletal remodeling, stress responses, and the activation of inflammatory cascades, all of which are closely linked to blood-brain barrier (BBB) dysfunction. The 2021 international expert consensus has abandoned the binary "A1/A2" classification, advocating instead for a "reactive continuum" perspective regarding astrocyte state transitions [17]. This implies that the same molecular biomarker can correspond to vastly different biological meanings depending on the microenvironment, temporal window, and comorbidity burden. Consequently, elevated GFAP levels cannot be directly or exclusively attributed to a fixed inflammatory phenotype.

The "vascular-inflammation axis" proposed in this review does not refer to a newly discovered anatomical structure, nor does it presume a confirmed, unified mechanistic chain; rather, it serves as a pathophysiological analytical framework awaiting validation. This framework emphasizes that, within the context of Alzheimer's disease (AD), vascular factors — centered on cerebral small vessel disease (CSVD) burden, BBB integrity, and endothelial-glial interactions — synergistically modulate astrocyte reactivity alongside Aβ/Tau pathology, ultimately mapping onto peripheral GFAP levels. Compared to the anatomical definition of the "neurovascular unit" (NVU), this framework focuses more heavily on pathophysiological coupling. Furthermore, compared to the broader concept of "neuroinflammation," it explicitly necessitates the incorporation of vascular backgrounds and their interactive effects into study designs and statistical analyses.

Recent single-cell and spatial transcriptomic studies have revealed the presence of disease-associated astrocyte subpopulations in the AD brain [18,19], characterized by complement activation, lipid metabolism remodeling, enhanced synaptic phagocytosis, and reciprocal amplification with microglia. Therefore, an elevation in GFAP tends to reflect a shared phenotype of an "activated reactive state" rather than acting as a specific indicator for a single pathological pathway. Reducing GFAP to a simple linear mapping of neuroinflammatory intensity faces multiple methodological limitations, including limited specificity, ambiguous spatial correspondence, and difficulties in polarity judgment. In other words, GFAP lacks a linear, uni-dimensional mapping significance for the intensity of intra-cerebral inflammation.

Addressing this interpretive dilemma, this review introduces the "vascular-inflammation axis" as an integrative analytical perspective. This framework does not deny the fundamental impact of Aβ and Tau on GFAP; instead, it underscores that CSVD burden, BBB status, and endothelial-glial crosstalk can significantly modulate the expression amplitude and clinical connotation of GFAP under an identical pathological background. Put differently, GFAP acts more as an integrated readout converging from multiple pathological inputs. Its levels must be interpreted through the interaction between the Aβ/Tau background and the vascular background, rather than being judged in isolation from the CSVD burden.

Current research provides preliminary biological support for this analytical framework. CSVD compromises BBB integrity through endothelial dysfunction, basement membrane thickening, pericyte loss, and cerebral hypoperfusion. Chronic ischemic and hypoxic environments activate signaling pathways that induce GFAP upregulation [12]. NVU studies further suggest that continuous crosstalk among endothelial cells, pericytes, astrocytes, and microglia collectively shapes the inflammatory microenvironment and BBB stability. Concurrently, activated microglia influence the reactive states of astrocytes via the release of signaling molecules [13].

4. Evidence Synthesis of GFAP Heterogeneity

4.1 Evidence in Late-Onset AD (LOAD)

In late-onset AD (LOAD), the correlation between GFAP and

Aβ pathology demonstrates high biological robustness, positioning the LOAD continuum as the primary empirical scenario for validating our three core propositions. Data from the ROS/MAP study indicate that cerebral GFAP expression correlates significantly with Aβ plaques, tau tangles, and cognitive impairment, with this effect exhibiting substantial regional heterogeneity [4]. Prior to our search cutoff, longitudinal evidence regarding the dynamic evolution of GFAP in LOAD remained relatively scarce. Supplementary studies published subsequently suggest that the rate of GFAP change may correlate with future cognitive decline and clinical progression risk; however, this signal necessitates further replication in larger prospective cohorts [5]. Consequently, LOAD serves as the principal evidence base for examining the three thematic dimensions, rather than merely acting as a parallel subtype to EOAD.

4.1.1 Dimension 1: Robustness of CSVD modulation effects

Current evidence suggests that CSVD burden may significantly modulate the pathological interpretive efficacy of GFAP. As summarized in Table 1, this represents "suggestive evidence requiring multicenter replication," reflecting a scientific signal with reproducible potential rather than a universally established law. Notably, this CSVD modulation effect may be particularly pronounced in East Asian populations. In a Singaporean Chinese cohort (Chong 2024), high WMH burden (Fazekas score of 3) decreased the area under the curve (AUC) of GFAP for identifying Aβ positivity from 0.82 to 0.71 [10]. This reduction was substantially more pronounced than that observed in the Dutch SMART-MR study, where the AUC only decreased from 0.78 to 0.74 [20]. This cross-population phenotypic divergence directly illustrates how heavier vascular backgrounds skew the pathological anchoring of GFAP, perfectly aligning with the "vascular-inflammation axis" framework. Emerging evidence from China (Jiao et al.) further substantiates this, revealing that the association between GFAP and Aβ-PET was significantly attenuated in the subgroup with moderate-to-severe WMH (Fazekas ≥ 2) (β=0.42 vs. 0.68, P=0.03) [21]. However, current domestic studies are predominantly single-center cross-sectional designs with substantial heterogeneity in imaging quantification methods (e.g., visual scoring versus volumetric measurements), remaining insufficient to establish unified regional reference thresholds. Future multicenter studies should pre-specify East Asian high-CSVD subgroups to determine optimal clinical cutoffs and comprehensive interpretation strategies combined with MRI.

4.1.2 Dimension 2: Independence from major confounders

It is imperative to determine whether the association between GFAP and vascular lesions remains robust after rigorously adjusting for major confounders. The SMART-MR study indicates an independent correlation between GFAP and cortical infarct burden (OR=1.45; 95% CI: 1.09-1.92), an association that is not entirely mediated by Aβ status [20]. Concurrently, Asian cohort studies confirm that the interpretive power of GFAP is significantly influenced by white matter lesion backgrounds, such as WMH. This highlights that the coupling relationship between GFAP and vascular phenotypes necessitates profound validation in broader populations employing more stringent covariate-adjusted statistical models.

4.1.3 Dimension 3: Temporal sequence support

Longitudinal studies offer preliminary empirical support for the temporal sequence among GFAP alterations, cognitive decline, brain atrophy, and parallel pathological evolutions. As of the search cutoff, the longitudinal evidence base in this domain remained sparse. Although subsequent supplementary studies suggest that the dynamic trajectory of GFAP correlates with the rate of cognitive decline and clinical progression risk [5], current limitations regarding follow-up duration, sample sizes, and external reproducibility persist. Consequently, Table 2 maintains a neutral interpretation of this proposition as possessing "preliminary longitudinal signals, insufficient for clinical extrapolation". While these findings hint at a temporal link between GFAP evolution and disease progression, existing evidence only supports its role as an accompanying signal of pathological activity, rather than an initiating factor in the causal chain.

4.2 Interpretive Boundaries in Early-Onset AD (EOAD)

The evidence base for early-onset AD (EOAD) is markedly sparser than that for LOAD. Thus, EOAD is positioned not as an equivalent parallel scenario, but rather as a supplementary context for validating GFAP's pathological sensitivity, genetic heterogeneity, and vascular modulation boundaries. It is crucial to distinguish autosomal dominant AD (ADAD) from sporadic EOAD; although both are early-onset, their genetic drivers, pathological timelines, and clinical extrapolation boundaries differ fundamentally. ADAD research demonstrates that plasma GFAP can elevate significantly years before expected symptom onset, correlating positively with Aβ pathology during the asymptomatic phase [6,22,23]. However, ADAD evidence cannot substitute for sporadic EOAD extrapolation. Evaluated against the three scientific propositions, the evidence chain for sporadic EOAD represents a critical area for future investigation to establish a comprehensive pathophysiological model. Regarding Dimension 1 (CSVD modulation), sporadic EOAD lacks robust, large-scale MRI-stratified data. For Dimension 2 (independence from confounders), existing studies are heavily confined to single-center cross-sectional designs, impeding adequate adjustment for disease stage, atrophy severity, and comorbidity burden. Addressing Dimension 3 (temporal sequence), long-term longitudinal follow-up data for sporadic EOAD are virtually nonexistent. The profound genetic heterogeneity of EOAD further complicates the biological interpretation of the GFAP signal. Beyond APP, PSEN1, and PSEN2 mutations, risk genes associated with immunity and lipid metabolism—such as TREM2 and ABCA7—may indirectly modulate GFAP expression by altering microglial-astrocytic crosstalk, Aβ clearance efficiency, and the inflammatory microenvironment [24]. Consequently, elevated GFAP in sporadic EOAD datasets may yield false-positive pathological interpretations if not meticulously adjusted for region-specific atrophy patterns (e.g., precuneus/parietal-dominant atrophy). To address the current paucity of evidence, future sporadic EOAD research designs must embrace two methodological imperatives. First, investigations should evolve beyond

merely describing "elevated expression levels" to synchronously integrating MRI vascular phenotypes, Aβ/tau pathological anchoring, and genetic stratification on a unified platform. This is essential to distinguish whether GFAP elevations reflect pathological intensity, regional brain vulnerability, or genetic drivers. Second, given the scarcity of EOAD samples, multicenter collaborations, pre-registered analyses, and external validations are urgently needed to mitigate selection bias inherent to single-center studies. From a research priority perspective, the immediate hurdle for sporadic EOAD is not establishing diagnostic cutoffs, but rather resolving three foundational scientific questions: first, the dynamic temporal relationship between GFAP and Tau-driven cortical neurodegeneration; second, whether GFAP retains stable Aβ pathological anchoring properties under low-CSVD backgrounds; and third, whether a reproducible regional mapping exists between GFAP levels and the precuneus/parietal-dominant atrophy pattern. Only when these core questions are robustly answered can EOAD evidence structurally align with LOAD.

5. Discussion and Clinical Implications

5.1 Comprehensive Judgment of Existing Evidence

Based on the current maturity of evidence, the statistical association between plasma GFAP and Alzheimer's disease (AD) pathology is relatively robust in the late-onset AD (LOAD) continuum. Evidence consistently demonstrates significant associations between elevated GFAP, increased amyloid-β (Aβ) burden, and accelerated cognitive decline, typically graded at OCEBM Level 2b. However, the "vascular-inflammation axis" remains an interpretative analytical framework rather than a confirmed causal mechanism. While GFAP links with vascular markers—such as white matter hyperintensities (WMH), cortical infarcts, or cerebral amyloid angiopathy (CAA)—are suggestive, significant inter-study heterogeneity precludes definitive meta-analytical estimation of effect sizes. Furthermore, evidence for sporadic early-onset AD (EOAD) remains critically sparse, and findings from autosomal dominant AD (ADAD) cannot be directly extrapolated to sporadic cases. Future research must resolve whether GFAP×CSVD interaction terms possess stable predictive utility and assess the incremental prognostic value of GFAP relative to p-tau217 in high-vascular-load subgroups. Currently, the framework's primary significance lies in guiding researchers to incorporate vascular backgrounds as an explicit effect modifier in experimental designs to mitigate circular reasoning.

5.2 Clinical Translation and Hierarchical Application

In clinical translation, plasma GFAP and p-tau217 exhibit significant complementarity: while p-tau217 excels in pathological staging [25], GFAP is more sensitive to astrocyte reactivity and vascular co-pathology. Consequently, GFAP is better positioned as an explanatory biomarker for risk stratification rather than a standalone diagnostic tool, as detailed in Table 3. To guide prudent interpretation, we propose the following 'Clinical Interpretative Guidelines': (1) no determination of diagnostic cut-offs without concurrent MRI-based vascular assessment; (2) no interpretation of absolute values in individuals with renal impairment (e.g., low eGFR); and (3) no direct equating of a single GFAP elevation with a linear increase in cerebral inflammatory intensity. Given the influence of analytical platforms and individual biological variations, GFAP thresholds should not be horizontally migrated across different populations without standardized bridge validation [26].

5.3 Methodological Value of East Asian Populations

The high prevalence of cerebral small vessel disease (CSVD) and mixed pathologies in East Asian populations [27,28] provides a critical real-world scenario for validating the vascular-inflammation axis. Regional evidence from Singaporean and Chinese cohorts suggests that heavy CSVD burden significantly attenuates the association between GFAP and Aβ pathological anchoring. This underscores the need for integrated "GFAP-MRI-CSVD" multidimensional models tailored to regional pathological characteristics rather than simply adopting Western diagnostic thresholds [29]. This scenario is particularly valuable for clarifying whether GFAP functions primarily as an Aβ-specific marker or as a comprehensive indicator of pathological activity and comorbidity burden. However, due to current evidence gaps, regional adaptation remains a reasonable scientific hypothesis rather than a settled conclusion.

5.4 Methodological Recommendations and Limitations

To transition from qualitative description to quantitative verification, future research must prioritize methodological rigor, with key imperatives summarized in Table 4. Pre-analytical standardization of sample handling—including EDTA plasma use, fasting status, and recording blood collection-to-centrifugation intervals—is paramount [30,31]. Vascular phenotyping must evolve beyond simple white matter scores to comprehensive metrics aligned with STRIVE-2 standards [32,33]. Statistical models should pre-specify interaction terms (e.g., GFAP×CSVD) and rigorously adjust for confounders, including age, APOE ε4 status, and renal function. Furthermore, researchers must account for biological variation (RCV, CVI) and avoid over-interpreting single-point elevations.

This study acknowledges several limitations, primarily the structural asymmetry of evidence favoring LOAD and the scarcity of longitudinal/pathological anchoring data. A critical interpretive boundary remains the risk of "reverse causality" [34]—where blood-brain barrier (BBB) breakdown precedes and induces peripheral GFAP leakage—rather than GFAP expression driving vascular injury [11]. Peripheral GFAP levels do not necessarily equate to intra-cerebral inflammatory intensity. Future research should integrate single-cell transcriptomics with longitudinal cohorts to elucidate astrocyte molecular signatures under varied vascular stressors [18,19], thereby maturing the "vascular-inflammation axis" into a predictive evidence model.

6. Conclusions

In summary, the dynamic evolution of plasma GFAP levels in Alzheimer's disease (AD) must be interpreted through a multidimensional integration of Aβ/Tau pathological burden

and the individual's vascular background. The "vascular-inflammation axis" should currently be regarded as an interpretative analytical framework for deciphering GFAP expression heterogeneity rather than a definitively established pathophysiological mechanism.

At present, the late-onset AD (LOAD) continuum remains the primary scenario for validating the modulatory effects of the vascular background on GFAP. However, the robustness of its associative effects independent of major covariates and the supporting longitudinal temporal evidence remain insufficient. Early-onset AD (EOAD), particularly sporadic cases, currently serves as a boundary scenario for evidence, and conclusions derived from autosomal dominant AD (ADAD) research should not be directly extrapolated to sporadic EOAD. Based on the current stage of evidence-based medicine, GFAP is best suited for inclusion in multi-marker evaluation systems for research-oriented risk stratification and heterogeneity interpretation. It is not yet sufficient to stand alone as a basis for routine clinical diagnostic classification, the establishment of unified cut-off values, or standardized clinical decision-making workflows.

The significant burden of cerebral small vessel disease (CSVD) in East Asian populations reflects ethnic-specific vascular profiles that provide a critical real-world scenario for validating the "vascular-inflammation axis" framework. Rather than simply adopting diagnostic thresholds established in Western populations, Chinese researchers should focus on constructing integrated "GFAP-MRI-CSVD" multidimensional assessment models. This approach is essential for developing precision evaluation tools specifically adapted to the regional pathological characteristics of elderly populations in East Asia.

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