



Correlation between cerebral small vessel disease neuroimaging biomarkers and plasma PlGF among Alzheimer’s disease and non-Alzheimer’s disease participants in memory clinic cohort in Thailand

Thanakit Pongpitakmetha^{1-4*}, Thanapoom Taweephol⁵, Thachamai Smitasiri^{3,6}, Sekh Thanprasertsuk^{3-4,6}, Adipa Chongsuksantikul⁷, Prawit Oangkhana⁷, Watayuth Luechaipanit⁷, Thanaporn Haethaisong⁷, Jedsada Khieukhajee⁸, Kittithatch Booncharoen^{3,9}, Yuttachai Likitjaroen^{4,10}, Poosanu Thanapornsangsuth^{2-3,7,11,12}

1 | Background

Cerebral small vessel disease (CSVD) is one of the main contributing factors to vascular cognitive impairment and dementia (VCID) in the aging population. CSVD can contribute to cognitive decline by itself or worsen cognitive decline as a co-pathology in Alzheimer’s disease (AD). Plasma placental growth factor (PlGF), a member of the vascular endothelial growth factor family, is a promising novel biomarker of subcortical white matter burden in both AD and non-AD populations. This study investigates the correlation between CSVD neuroimaging biomarkers and plasma PlGF in a memory clinic setting.

2 | Method

The clinical information and plasma biomarkers were collected from memory clinic cohorts. Patients were categorized into AD and non-AD groups based on either an abnormal cerebrospinal fluid Amyloid beta (Aβ) 42/p-tau181 ratio, or a positive Aβ Positron Emission Topography (PET). **PlGF** was measured by using Human PlGF Quantikine ELISA Kit R&D Systems, part of Bio-Techne. **Magnetic resonance imaging (MRI)** was independently visual rated by the two trained investigators (TP, TT) using STRIVE-2 criteria (*Dueling M, 2023*). The validated composite total CSVD score (*Staals J, 2014*) ranging from 0-4 was calculated. The non-parametric statistical analysis was applied to analyze.

3 | Result

A total of 114 participants were enrolled. Clinical information, laboratory test results, and neuroimaging biomarkers were compared between AD and non-AD groups, as shown in **Table 1**. Plasma PlGF did not show a statistically significant difference between AD and non-AD groups. The Spearman’s correlation and the Wilcoxon rank sum test between plasma PlGF and each CSVD neuroimaging biomarker are summarized in **Table 2**. Plasma PlGF did not show a statistical correlation with CSVD scores or any of the CSVD neuroimaging biomarkers.

Total CSVD (point 0-4) = 4 items (1 point if present)

- 1) Presence of lacunes was defined as the presence of one or more lacunes
- 2) Presence of CMBs was defined as the presence of one or more CMBs
- 3) Presence of EPVS was counted if there were moderate to severe (grade 2–4) EPVS in the basal ganglia
- 4) Presence of WMH was defined as either (early) confluent deep WMH (Fazekas score 2 or 3) or irregular periventricular WMH extending into the deep white matter (Fazekas score 3)

Plasma PlGF was NOT associated with MRI markers of CSVD or total CSVD burden in this memory clinic cohort. These findings suggest *limited* utility of plasma PlGF as a standalone biomarker of CSVD.

TABLE 1 Baseline characteristics (clinical, laboratory, and neuroimaging biomarkers)

	Non-AD (N = 52)	AD (N = 62)	Overall (N=114)	p-value
Age (year)	60.0 [34.0, 70.0]	70.5 [60.8, 75.0]	63.0 [46.0, 74.0]	0.355
Female (%)	36 (69.2%)	45 (72.6%)	81 (71.1%)	0.836
Hypertension (%)	25 (48.1%)	23 (37.1%)	48 (42.1%)	0.258
Diabetes mellitus (%)	13 (25.0%)	8 (12.9%)	21 (18.4%)	0.145
Dyslipidemia (%)	24 (46.2%)	22 (35.5%)	46 (40.4%)	0.258
History of symptomatic stroke (%)	4 (7.7%)	2 (3.2%)	6 (5.3%)	0.409
Chronic kidney disease (%)	5 (9.6%)	3 (4.8%)	8 (7.0%)	0.466
Duration of symptoms (months)	26.0 [6.0, 49.0] (N = 51, 91%)	42.5 [27.0, 65.0]	37.0 [21.0, 59.0] (N = 113, 99%)	< 0.001***
Clinical stages (%)				< 0.001***
CU/SCD	13 (25.0%)	0 (0%)	13 (11.4%)	
MCI	21 (40.4%)	31 (50.0%)	49 (43.0%)	
Dementia	18 (34.6%)	31 (50.0%)	52 (45.6%)	
Fluid biomarkers				
Plasma PlGF (pg/ml)	21.68 [14.21, 37.00]	19.35 [10.00, 31.45]	21.17 [11.93, 35.20]	0.242
Log plasma PlGF	3.08 [2.65, 3.61]	2.96 [2.30, 3.45]	3.05 [2.48, 3.56]	0.242
Plasma GFAP (pg/ml)	156.73 [110.47, 250.86]	275.11 [200.61, 392.80]	220.12 [135.09, 355.46]	< 0.001***
Log plasma GFAP (Mean, SD)	5.17 (0.81)	5.63 (0.67)	5.42 (0.77)	< 0.001***
Plasma p-tau 217 (pg/ml)	4.79 [3.15, 6.97] (N = 51, 98%)	16.39 [10.72, 26.83]	8.95 [4.92, 18.79] (N = 113, 99%)	< 0.001***
Log plasma p-tau 217	1.57 [1.15, 19.4] (N = 51, 98%)	2.80 [2.37, 3.29]	2.19 [1.59, 2.93] (N = 113, 99%)	< 0.001***
Plasma p-tau181 (pg/ml)	1.94 [1.46, 2.68] (N=26, 50%)	3.07 [2.58, 4.50] (N = 15, 24%)	2.34 [1.63, 3.37] (N = 41, 36%)	0.006**
Log plasma p-tau181 (Mean, SD)	0.26 (0.49)	1.16 (0.48)	0.86 (0.53)	0.006**
CSF amyloid-beta 42/p-tau 181 [cut-off from Gaussian mixture models of 13.2]	34.81 [22.85, 45.27] (N=26, 50%)	5.78 [4.50, 7.27] (N = 15, 24%)	20.38 [6.82, 37.02] (N = 41, 36%)	< 0.001***
Amyloid-beta PET positive	0 (0%) (N = 24, 46%)	46 (100%) (N=46, 74%)	46 (40%) (N=70, 61%)	< 0.001***
Plasma NFL (pg/ml)	21.26 [13.83, 30.65] (N = 51, 45%)	18.95 [14.22, 24.80]	19.68 [14.00, 26.91] (N=113, 99%)	0.434
Log plasma NFL	3.06 [2.63, 3.42] (N = 51, 45%)	2.94 [2.65, 3.21]	3.06 [2.63, 3.42] (N=113, 99%)	0.434
CSVD biomarkers				
Total CSVD *	0	14 (26.9%)	7 (11.3%)	21 (18.4%)
0	14 (26.9%)	7 (11.3%)	21 (18.4%)	0.018*
1	11 (21.2%)	26 (41.9%)	37 (32.5%)	
2	9 (17.3%)	15 (24.2%)	24 (21.1%)	
3	13 (25.0%)	13 (21.0%)	26 (22.8%)	
4	5 (9.6%)	1 (1.6%)	6 (5.3%)	
Total CSVD score (ordinal scale)	2 [0, 3]	1 [1, 2]	1 [1, 3]	0.828
EPVS or DPVS (per hemisphere) at basal ganglia (%)	0 (0%)	0 (0%)	0 (0%)	0.336
0 EPVS/hemisphere (absence)	0 (0%)	0 (0%)	0 (0%)	
1-10 EPVS/hemisphere (mild)	34 (65.4%)	39 (62.9%)	73 (64.0%)	
11-20 EPVS/hemisphere (moderate)	15 (28.8%)	19 (30.6%)	34 (29.8%)	
21-40 EPVS/hemisphere (frequent)	1 (1.9%)	4 (6.5%)	5 (4.4%)	
> 40 EPVS/hemisphere (severe)	2 (3.8%)	0 (0%)	2 (1.8%)	
EPVS or DPVS (per hemisphere) at centrum semiovale (%)	0 (0%)	0 (0%)	0 (0%)	0.159
0 EPVS/hemisphere (absence)	5 (9.6%)	1 (1.6%)	6 (5.3%)	
1-10 EPVS/hemisphere (mild)	9 (17.3%)	16 (25.8%)	25 (21.9%)	
11-20 EPVS/hemisphere (moderate)	26 (50.0%)	26 (41.9%)	52 (45.6%)	
21-40 EPVS/hemisphere (frequent)	12 (23.1%)	19 (30.6%)	31 (27.2%)	
> 40 EPVS/hemisphere (severe)				
Total WMH Fazekas score (%)				0.638
0	1 (1.9%)	0 (0%)	1 (0.9%)	
1	2 (3.8%)	4 (6.5%)	6 (5.3%)	
2	18 (34.6%)	26 (46.8%)	47 (41.2%)	
3	10 (19.2%)	9 (14.5%)	19 (16.7%)	
4	12 (23.1%)	11 (17.7%)	23 (20.2%)	
5	4 (7.7%)	2 (3.2%)	6 (5.3%)	
6	5 (9.6%)	7 (11.3%)	12 (10.5%)	
Periventricular WMH Fazekas score (%)	0	1 (1.9%)	0 (0%)	0.322
0	27 (51.9%)	41 (66.1%)	68 (59.6%)	
1	17 (32.7%)	14 (22.6%)	31 (27.2%)	
2	7 (13.5%)	7 (11.3%)	14 (12.3%)	
3				
Subcortical WMH Fazekas score (%)	0	3 (5.8%)	4 (6.5%)	0.741
0	21 (40.4%)	30 (48.4%)	51 (44.7%)	
1	21 (40.4%)	19 (30.6%)	40 (35.1%)	
2	7 (13.5%)	9 (14.5%)	16 (14.0%)	
3	58 (50.9%)	31 (50.0%)	27 (51.0%)	0.853
Multiple subcortical WMH (> 10 spots) (%)	24 (46.2%)	23 (37.1%)	47 (41.2%)	0.346
Presence of lacunes (%)				0.699
Total CMBs	1-5 (%)	34 (29.8%)	19 (30.6%)	15 (28.8%)
1-5 (%)	> 5 (%)	9 (7.9%)	6 (9.7%)	3 (5.8%)
Lobar CMBs	1-5 (%)	22 (19.3%)	11 (17.7%)	11 (21.2%)
1-5 (%)	> 5 (%)	9 (7.9%)	6 (9.7%)	3 (5.8%)
Deep CMBs	1-5 (%)	10 (8.8%)	6 (9.7%)	4 (7.7%)
1-5 (%)	> 5 (%)	1 (0.9%)	0 (0%)	1 (1.9%)
Cerebellar CMBs	1-5 (%)	6 (11.5%)	8 (12.9%)	14 (12.3%)
1-5 (%)	> 5 (%)	0 (0%)	1 (1.6%)	1 (0.9%)
cSS				0.7256
Focal (1-3 foci) (%)	3 (6.1%)	5 (8.8%)	8 (7.0%)	ner's test for
Disseminated (>3 foci) (%)	0 (0%)	0 (0%)	0 (0%)	< 0.001***
Gadolinium enhancement (%)				
Not performed	31 (59.6%)	56 (90.3%)	87 (76.3%)	
Absence	14 (26.9%)	5 (8.1%)	19 (16.7%)	
Presence	7 (13.5%)	1 (1.6%)	8 (7.0%)	

TABLE 2 The correlation between cerebral small vessel disease neuroimaging biomarkers and plasma placental growth factor

	Non-AD (N = 52)	AD (N = 62)	Overall (N=114)
Total CSVD score ^a	0.04 (0.757)	-0.01 (0.968)	0.03 (0.750)
EPVS at basal ganglia	0.03 (0.828)	0.175 (0.173)	0.11 (0.241)
EPVS at centrum semiovale	0.10 (0.465)	0.24 (0.061)	0.17 (0.069)
Total WMH Fazekas score	-0.08 (0.561)	0.06 (0.650)	0.01 (0.950)
Periventricular WMH Fazekas score	-0.14 (0.336)	0.02 (0.873)	-0.05 (0.628)
Subcortical WMH Fazekas score	-0.04 (0.801)	0.06 (0.653)	0.02 (0.811)
Multiple subcortical WMH spot	-0.11 (0.421)	0.05 (0.687)	-0.02 (0.815)
Presence of lacunes	0.03 (0.828)	-0.11 (0.390)	-0.04 (0.678)
Total CMBs	0.06 (0.671)	-0.16 (0.208)	-0.07 (0.450)
Lobar CMBs	-0.03 (0.808)	-0.12 (0.367)	-0.08 (0.384)
Deep CMBs	0.08 (0.569)	0.05 (0.716)	0.07 (0.471)
Cerebellar CMBs	0.02 (0.912)	-0.20 (0.128)	-0.12 (0.198)
cSS	0.00 (0.977)	0.00 (0.984)	0.00 (0.966)
Presence of gadolinium enhancement [Wilcoxon rank sum test with continuity correction: W (p-value)]	56 (0.636)	4 (0.667)	92 (0.418)

Note: Unless specified, values are presented as Spearman's rank correlation: rho (p-value)
p-value* < 0.05, ** < 0.01, *** < 0.001
Abbreviations: AD = Alzheimer's disease, CMBs = cerebral microbleeds; cSS = cortical superficial siderosis; CSVD = cerebral small vessel disease; EPVS = enlarged perivascular space; EPVS = enlarged perivascular space; PlGF = placental growth factor; WMH = white matter hyperintensities

4 | Conclusion

Plasma PlGF showed similar values between AD and non-AD groups. Neither CSVD biomarkers nor total CSVD score correlated with plasma PlGF. These findings showed a limitation of measuring plasma PlGF as a solitary biomarker of CSVD burden in both AD and non-AD participants in a memory clinic setting. Further evaluation of the relationship between PlGF and quantitative volumetric white matter hypertensities should be explored.

Contact

Thanakit Pongpitakmetha, MD, MSc
Department of Pharmacology, Faculty of Medicine,
Chulalongkorn University
1873 Rama IV Road, Pathumwan, Bangkok,
Thailand 10330
Tel: +6622564481 https://pharma.md.chula.ac.th/
Email: thanakit.p@chula.md, thanakit.p@chula.ac.th

References

1. Dueling M, et al. Lancet Neurology. 2023 Sep;22(9):e10.
2. Staals J, et al. Neurology. 2014;83(14):1228-1234
3. Taweephol, et al. JAD. 2025; 104(2):325-330.

Funding

- The Health Systems Research Institute, Thailand (#64-027, #65-034, #66-121, #67-154).
 - Grants for development of new faculty staff, Ratchadaphiseksomphot Fund, Chulalongkorn University (Funding number: DNS_67_049_3000_011).
 - Research grant for neurologist, the Neurological Society of Thailand (NST)
- Funding number: 3/2567).



Affiliations

1. Department of Pharmacology, Faculty of Medicine, Chulalongkorn University, Bangkok, 10330, Thailand
2. Chula Neuroscience Center, King Chulalongkorn Memorial Hospital, The Thai Red Cross Society, Bangkok, 10330, Thailand.
3. Memory Clinic, King Chulalongkorn Memorial Hospital, The Thai Red Cross Society, Bangkok, 10330, Thailand.
4. Comprehensive Headache and Orofacial Pain (CHOP) Service and Research Group, Faculty of Medicine, Chulalongkorn University, Bangkok, 10330, Thailand.
5. Neurological Institute, University Hospitals Cleveland Medical Center, Case Western Reserve University, Cleveland, Ohio, 44106, USA.
6. Department of Physiology, Faculty of Medicine, Chulalongkorn University, Bangkok, 10330, Thailand

7. Thai Red Cross Emerging Infectious Diseases Health Science Centre, King Chulalongkorn Memorial Hospital, The Thai Red Cross Society, Bangkok, 10330, Thailand.
8. Department of Neurology, Neurological Institute of Thailand, Bangkok, 10400, Thailand
9. Center for Medical Excellence, Faculty of Medicine, Chiangmai University, Chiangmai, 50200, Thailand
10. Neurocognitive Unit, Division of Neurology, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand.
11. Division of Neurology, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand.
12. Global Brain Health Institute, University of California, San Francisco, San Francisco, CA, USA