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在线全文

•青年编委专栏•

血浆磷酸化-tau217等生物标志物对四川德阳地区人群认知功能障碍的诊断价值*

赖婉琳，夏逸林，傅宇童，黄子介，杨 超，王 越，李德波，陈 蕾△
四川大学华西医院 神经内科/高原健康联合研究所（成都 610041）

【摘要】 **目的** 阿尔茨海默病（Alzheimer disease, AD）是一个连续的疾病谱，有症状的阶段包括轻度认知障碍（mild cognitive impairment, MCI）时期、痴呆时期（又称AD痴呆）。本研究聚焦于MCI和AD痴呆的筛查，即AD疾病谱的筛查，分析血浆生物标志物对四川德阳地区人群认知功能障碍的诊断价值，为认知功能障碍的早筛早诊提供证据。**方法** 2023年8–10月对四川德阳地区50岁及以上人群进行问卷调查。调查内容包括人口学信息、病史信息、认知功能评估。将MCI患者纳入MCI组，将AD痴呆患者纳入AD组，其余为健康对照（healthy controls, HC）组。对部分抽样（所有AD痴呆患者、随机抽样的MCI患者及HC）采用我国自主研发的超灵敏数字免疫芯片技术检测血浆磷酸化-tau217（phosphorylated tau217, p-tau217）等4种认知相关生物标志物，采用淀粉样蛋白-β（amyloid beta, Aβ）分子探针的正电子发射断层显像（positron emission tomography, PET）检测受试者（所有AD患者及部分MCI患者）的Aβ沉积情况，评估上述血浆生物标志物对认知功能障碍的诊断价值。**结果** 本研究共调查受试者2 833人，其中AD痴呆患者30人（1.1%），MCI患者437人（15.4%），HC 2 366人（83.5%）。对30名AD痴呆患者、50名MCI患者、35名HC进行了4种血浆生物标志物检测。其中，血浆p-tau217区分AD痴呆与HC、AD痴呆与MCI的效果最好，受试者操作特征曲线下面积（area under the curve, AUC）分别为0.96〔95%置信区间（confidence interval, CI）0.91～1.00〕和0.93（95%CI 0.87～0.98）。AD痴呆、MCI、HC三组血浆p-tau217水平分别为（2.32±1.27）pg/mL、（0.54±0.45）pg/mL、（0.42±0.19）pg/mL，差异有统计学意义（P<0.000 1）。共纳入36名患者进行Aβ PET检测，其中，p-tau217诊断Aβ沉积效果最佳（AUC：0.99，95%CI 0.96～1.00）。Aβ沉积患者血浆p-tau217水平〔（2.52±1.17）pg/mL〕高于Aβ无沉积患者〔（0.53±0.19）pg/mL〕，差异有统计学意义（P<0.000 1）。血浆p-tau217水平与额、颞、枕叶的多个脑区Aβ PET摄取值呈正相关（r>0.70，P<0.000 1）。**结论** 采用国产自主研发技术检测血浆标志物能较好地诊断AD痴呆，尤其是血浆p-tau217诊断价值最高，或可推广用于人群的AD痴呆筛查。

【关键词】 阿尔茨海默病 轻度认知障碍 痴呆 Aβ分子探针 免疫芯片

Diagnostic Value of Phosphorylated tau217 and Other Plasma Biomarkers for Cognitive Dysfunction in the Populations of Deyang City, Sichuan Province, China

LAI Wanlin, XIA Yilin, FU Yutong, HUANG Zijie, YANG Chao, WANG Yue, LI Debo, CHEN Lei△. *Department of Neurology/Joint Research Institute of Altitude Health, West China Hospital, Sichuan University*, Chengdu 610041, China
△ Corresponding author, E-mail: leilei_25@126.com

【**Abstract**】 **Objective** Alzheimer disease (AD), a continuous disease spectrum, includes the symptomatic stages of the period of mild cognitive impairment (MCI) and the dementia period, also known as AD dementia. Focusing on MCI and AD dementia screening, i.e., AD spectrum screening, we analyzed the value of plasma biomarkers for diagnosing cognitive dysfunction in the local populations of Deyang City, Sichuan Province, China to provide evidence for the early screening and diagnosis of cognitive dysfunction. **Methods** A questionnaire survey was conducted between August 2023 and October 2023 among people aged 50 years or older in Deyang City, Sichuan Province. The survey covered demographic information, information on medical history, and cognitive function assessment. Subjects with MCI were included in the MCI group, those with AD dementia were included in the AD group, and the others were included in the healthy controls (HC) group. A partial sample, including all patients with AD dementia and a randomized sample of MCI patients and HC, was drawn. Then, the plasma levels of four cognition-related biomarkers, including phosphorylated tau217 (p-tau217), were measured using an ultrasensitive digital chip immunoassay technology independently developed in China. Amyloid beta (Aβ) deposition was determined by positron emission tomography (PET) using Aβ molecular probes in all AD dementia patients and some of the MCI patients. The diagnostic value of the plasma biomarkers for cognitive dysfunction was assessed. **Results** A total of 2 833 subjects were investigated, including 30 (1.1%) with AD dementia, 437 (15.4%) with MCI, and 2 366 (83.5%) with HC. We measured the plasma levels of 4 biomarkers of 30 AD dementia patients, 50 MCI patients, and 35 HC. Plasma p-tau217 performed best in differentiating AD dementia from HC and MCI, with the area under the curve (AUC) of receiver operator characteristic curves being 0.96 (95% CI: 0.91-1.00) and 0.93 (95% CI: 0.87-0.98), respectively. Plasma p-tau217 levels in the AD dementia, MCI, and HC groups were

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△ 通信作者，E-mail: leilei_25@126.com
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(2.32±1.27), (0.54±0.45), and (0.42±0.19) pg/mL, respectively, and the difference was statistically significant (P<0.000 1). A total of 36 patients underwent Aβ PET examination. Plasma p-tau217 showed the best performance in the diagnosis of Aβ deposition (AUC: 0.99, 95% CI: 0.96-1.00). Plasma p-tau217 levels were higher in Aβ-deposition-positive patients ([2.52±1.17] pg/mL) than those in Aβ-deposition-negative patients ([0.53±0.19] pg/mL), and the difference was statistically significant (P<0.000 1). Plasma p-tau217 levels were significantly and positively correlated with Aβ PET uptake values in multiple brain regions of the frontal, temporal, and occipital lobes (r>0.70, P<0.000 1). **Conclusion** Plasma biomarkers measured with a technology independently developed in China demonstrate good performance in diagnosing AD dementia. Plasma p-tau217, in particular, demonstrates the highest diagnostic value and can be used for AD dementia screening of large populations.

【Key words】 Alzheimer disease　Mild cognitive impairment　Dementia　Aβ molecular probes　Immunochip

据一项46 011人的全国性研究报道，我国60 岁以上人群中痴呆的患病率约为6.0%，90岁以上痴呆患病率达到30%[1]。2019年，我国由痴呆造成的经济负担已达到了1950亿美元(约合人民币1.35万亿元)[2]。阿尔茨海默病(Alzheimer disease, AD)是痴呆最常见的病因，据估计，我国AD患者超过980万[1]。AD是一个连续的疾病谱，有症状的阶段包括轻度认知障碍(mild cognitive impairment, MCI)时期(有前驱症状的AD)、痴呆时期(AD痴呆)。当患者进入AD痴呆时期时，病程将不可逆转。因此AD痴呆的管理有赖于“早期发现、早期介入”[3]。

目前检测MCI和AD痴呆的方法主要包括认知功能评估、分子影像学检查、脑脊液病理检测。认知功能评估如简易精神状态检查(mini-mental state examination, MMSE)受年龄、教育、地理和文化差异等许多因素的影响[4-6]。淀粉样蛋白-β(amyloid-beta, Aβ)和tau蛋白的正电子发射断层扫描(positron emission tomography, PET)虽然直观和准确，但成本高且缺乏动态监测能力。腰椎穿刺脑脊液(cerebrospinal fluid, CSF)检测Aβ和tau具有侵入性，也不适合大规模人群筛查[7]。近年来，国际上报道采用血浆磷酸化-tau217 (phosphorylated tau217, p-tau217)、磷酸化-tau181(phosphorylated-tau181, p-tau181)、神经纤维丝轻链(neurofilament light chain, NfL)及胶质纤维酸性蛋白(glial fibrillary acidic protein, GFAP)等标志物诊断AD痴呆时具有良好的准确性，受试者操作特征(receiver operator characteristic, ROC)曲线下面积(area under the curve, AUC)达到0.8 ~ 0.9[8-10]。然而，这些标志物在区分MCI和健康个体时模型AUC为0.54 ~ 0.79，准确性较低[8,11-13]。而且，目前这些标志物的诊断效果在我国的研究较少，且检测依赖于成本较高的进口试剂盒，检测费用昂贵，不适用于大样本人群的筛查。

2020年第七次全国人口普查结果显示，全国60岁及以上人口占辖区人口比重超过20%的省份主要集中在东北、川渝等地区。而在川渝地区中，德阳60岁及以上人口占比达到25%，超过全国(18.7%)和川渝(21.7%)平均水平，是人口老龄化最典型的区域之一。基于此，本研究在四川德阳地区人群中采用我国自主研发的超灵敏数字免疫芯片技术进行血浆标志物的检测，分析其对认知功能障碍的诊断价值，为AD的早期筛查防治提供参考依据。

1　资料与方法

1.1　研究对象

本研究于2023年8–10月对四川德阳地区人群进行问卷调查。调查人群纳入标准：年龄50岁及以上。排除标准：耳聋、偏瘫、失明等无法配合的人群；独居老人、患恶性肿瘤以及重大慢性疾病(如严重的心脏功能不全、肺功能不全、肝功能不全)人群。调查内容包括人口学信息、病史信息、认知功能评估。将MCI患者纳入MCI组，将AD痴呆患者纳入AD组，其余为健康对照(healthy controls, HC)组。对参与调查的所有AD痴呆患者、随机抽样的MCI患者及HC进行血浆p-tau217、p-tau181、NfL、GFAP等4种认知相关生物标志物检测，评估血浆生物标志物对认知功能障碍的诊断价值。所有AD组患者(30名)均完成了Aβ PET检测以确诊；50名MCI组患者中6名患者完成了Aβ PET检测。本研究经四川大学华西医院医学伦理学委员会批准，批准号：2023年审(1346)号，所有受试者均已签署知情同意书。

1.2　研究方法

1.2.1　受试者纳入及基线资料采集

采用标准表格对受试者进行基线资料的采集，包括性别、年龄等人口学基本信息；家族史、目前所患慢性疾病以及长期服用药物信息。调查员均为经过专业培训的科研人员，与受试者进行面对面访谈。

1.2.2　认知功能评估及诊断

评估内容包括简易精神状态检查量表(the Mini-Mental State Examination, MMSE)评分和蒙特利尔认知评估量表(the Montreal Cognitive Assessment, MoCA)评分，量表由临床医生或医学护士经过培训合格后对受试者进行评估。当MMSE量表评分≤27分则进一步由两名

神经专科医生参照2018中国痴呆与认知障碍诊治指南(一):痴呆及其分类诊断标准[14]、2018中国痴呆与认知障碍诊治指南(五):轻度认知障碍的诊断与治疗[15]进行AD痴呆和MCI的诊断。如两名神经专科医生之间有歧义,则由第三名高级神经内科医生进行确诊。如第三名医生仍不能确诊,则将该样本进行排除。本研究聚焦于MCI和AD痴呆的筛查,都属于AD疾病谱的筛查。

1.2.3 血浆样本采集及生物标志物检测

对30名AD组患者、50名MCI组患者、35名HC进行了4种血浆生物标志物检测。早上8:00–10:00采集受试者空腹8 h以上静脉血于乙二胺四乙酸(ethylene diamine tetraacetic acid, EDTA)管中,4 ℃,2 000×g离心10 min。血浆p-tau217、p-tau181、NfL、GFAP定量检测采用超灵敏数字免疫芯片技术在格物致和自动化Inspirer-DX平台上完成。标准曲线设置为两重复检测,拟合的标准曲线r均不低于0.99,符合质控要求。

1.2.4 Aβ蛋白分子影像探针检测

共纳入36名患者进行Aβ蛋白分子影像探针检测。通过Aβ PET检测受试者的Aβ沉积情况。PET检查当日,受试者于检查前均在安静状态下休息至少30 min,尽量排空膀胱,检查过程中全程保持清醒状态,仰卧。显像剂为18F-AV45,注射剂量为370 MBq (10 mCi),注射体积小于10 mL,注射部位为一侧上肢肘部静脉。测量标准化摄取值比(standard uptake value ratio, SUVR),为各脑区与小脑皮质摄取比值。

1.3 统计学方法

采用SPSS 26.0及Prism 6进行数据的统计学处理分析及作图。计数资料以频数和百分比表示,计量资料以$\bar{x}\pm s$或中位数(四分位间距)表示,采用t检验或方差分析进行组间比较分析。分别绘制4种血浆标志物受试者工作特征(the receiver operating characteristic, ROC)曲线,以分析血浆标志物对认知功能障碍的诊断价值。采用Pearson相关系数计算各脑区SUVR与4种血浆标志物的相关性。$P<0.05$为差异有统计学意义。

2 结果

2.1 基线特征

本次研究共调查2 833人,年龄50~85岁,女性1 899人(67.0%),男性934人(33.0%)。受试者平均年龄(63.6±8.1)岁,中位年龄63.0岁,其中AD组患者30人(1.1%),MCI组患者437人(15.4%),HC组2 366人(83.5%)。其中,进行血浆标志物检测的AD组30人,MCI组50人,HC组35人。3组之间年龄差异有统计学意义($P=0.002$),性别比例差异无统计学意义。见表1。

表 1 三组人群基线特征比较

Table 1 Comparison of the basic characteristics of the three groups

Characteristic	HC group (*n*=35)	MCI group (*n*=50)	AD group (*n*=30)	*P*
Age/yr., $\bar{x}\pm s$	64.7±6.3	67.3±6.5	70.6±6.3	0.002
Sex/case (%)				0.752
Male	13 (37.1)	15 (30.0)	9 (30.0)	
Female	22 (62.9)	35 (70.0)	21 (70.0)	

HC: healthy controls; MCI: mild cognitive impairment; AD: Alzheimer disease. Those with AD dementia were included in the AD group.

2.2 血浆标志物水平与认知功能障碍

见图1。血浆p-tau217水平(pg/mL)AD组(2.32±1.27)高于MCI组(0.54±0.45)及HC组(0.42±0.19),差异均有统计学意义($P<0.000\,1$)。血浆p-tau181水平(pg/mL)AD组(2.21±1.01)高于MCI组(1.07±0.82)及HC组(0.92±0.43),差异均有统计学意义($P<0.000\,1$)。血浆NfL水平(pg/mL)AD组(12.15±7.92)高于MCI组(7.05±3.57, $P<0.001$)及HC组(5.61±2.60, $P<0.000\,1$),差异均有统计学意义。血浆GFAP水平(pg/mL)AD组(256.70±264.70)高于MCI组(108.20±78.90)及HC组(113.00±195.60),差异均有统计学意义($P<0.000\,1$)。分别用4种标志物水平绘ROC曲线,发现血浆p-tau217区分AD组与HC组、AD组与MCI组的效果最佳,曲线下面积(area under the ROC, AUC)分别为0.96〔95%置信区间(confidence interval, CI)0.91~1.00〕和0.93(95%CI 0.87~0.98)。血浆NfL区分MCI组与HC组效果最佳,AUC为0.63(95%CI 0.51~0.75)。

2.3 血浆标志物水平与Aβ PET结果

见图2。共纳入36名患者进行Aβ PET检测。其中Aβ无沉积9例(MCI组:4例;AD组:5例),Aβ沉积27例(MCI组:2例;AD组:25例)。Aβ沉积患者血浆p-tau217(pg/mL)〔(2.52±1.17) vs. (0.53±0.19), $P<0.000\,1$〕、p-tau181(pg/mL)〔(2.32±0.90) vs. (0.98±0.89), $P<0.001$〕、NfL(pg/mL)〔(12.58±7.93) vs. (8.47±5.34), $P<0.01$〕、GFAP(pg/mL)〔(263.30±277.30) vs. (110.80±85.07), $P<0.05$〕水平均高于Aβ无沉积患者,差异有统计学意义。分别用4种标志物水平绘制ROC,发现p-tau217诊断Aβ沉积效果最佳(AUC: 0.99, 95%CI 0.96~1.00),其次是p-tau181(AUC: 0.90, 95%CI 0.71~1.00)。

2.4 血浆标志物水平与Aβ PET摄取量相关性分析

见图3。计算各脑区SUVR与4种血浆标志物的相关性,结果发现血浆p-tau217、p-tau181水平与额叶、颞叶、枕叶的多个脑区SUVR显著正相关,p-tau217相关性最强。其中,SUVR与血浆p-tau217水平相关性最强的脑区

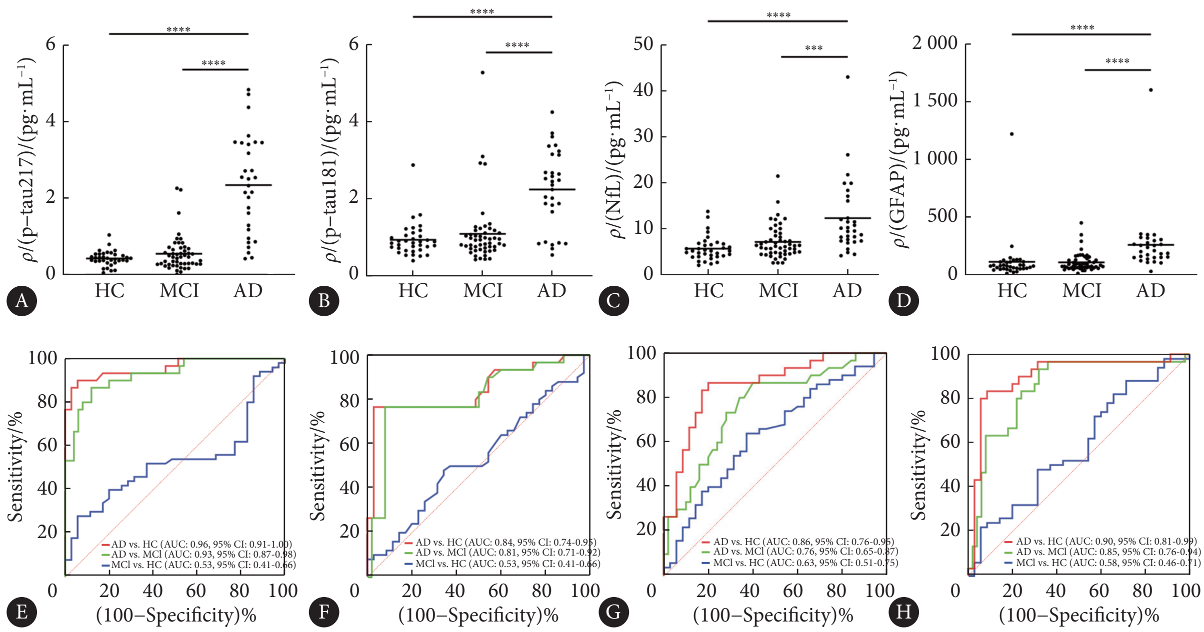

图 1 血浆标志物水平与认知功能障碍

Fig 1 Plasma biomarker levels and cognitive dysfunction

HC: healthy controls; MCI: mild cognitive impairment; AD: Alzheimer disease. Those with AD dementia were included in the AD group. p-tau217: phosphorylated tau217; p-tau181: phosphorylated-tau181; NfL: neurofilament light chain; GFAP: glial fibrillary acidic protein; AUC: area under the ROC; CI: confidence interval. The top row shows plasma levels of p-tau217 (A), p-tau181 (B), NfL (C), and GFAP (D) in the three groups. The bottom row shows the diagnostic effect of plasma p-tau217 (E), p-tau181 (F), NfL (G), and GFAP (H) on cognitive dysfunction. $^{***}P<0.001$, $^{****}P<0.0001$.

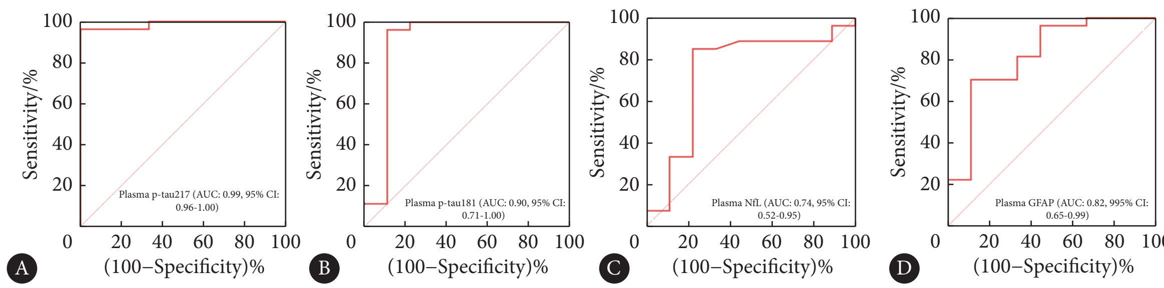

图 2 血浆p-tau217 (A)、p-tau181 (B)、NfL (C)、GFAP (D)对Aβ PET结果（Aβ沉积与否）的诊断效果

Fig 2 The diagnostic effect of plasma p-tau217 (A), p-tau181 (B), NfL (C), and GFAP (D) for Aβ PET results (presence or absense of Aβ deposition)

为左侧眶部额中回、右侧枕中回、右侧眶部额中回、右侧缘上回、右侧角回、右内侧额上回、右侧额中回、左侧颞中回、右侧颞中回、左侧枕中回、左侧额中回（$r>0.70$, $P<0.0001$）。

3　讨论

传统的认知评估量表易受到多种因素的干扰而影响评估结果，而PET或腰椎穿刺CSF检测AD生物标志物的方法是侵入性的，且价格昂贵，通常难以获取，高性能且基于外周血的生物标志物检测可能是高危人群早筛及患者病情监测的合适替代方法。随着美国国家老龄化研究所和阿尔茨海默病协会2023年标准修订，p-tau217、p-tau181、p-tau231已成为公认的AD生物标志物[16]。研究发现，不同的tau生物标志物出现异常的时间不同，p-tau181、p-tau217和p-tau231可在AD临床前期与Aβ PET同时出现异常，远早于tau PET[17-20]。这提示特定残基（181、217和231）磷酸化的N端片段的分泌可能代表了对β-淀粉样斑块的生理反应[21]。相比之下，其他tau标志物则在更晚些时候变得异常，其与tau PET的相关性比其与Aβ PET的相关性更好[22-23]。而血浆p-tau217由于表现出与CSF相当的准确性，已然成为目前最适合诊断、反映预后及生物学治疗效果的血浆AD生物标志物[16, 24-26]。

因此，近两年p-tau217在血液检测上备受关注。多篇文章已经报道血液中的p-tau217在临床诊断AD和非AD上准确度极高[24, 27-29]。本研究首次采用国内自主研发的技术对HC、MCI、AD痴呆3组人群的血浆样本进行了

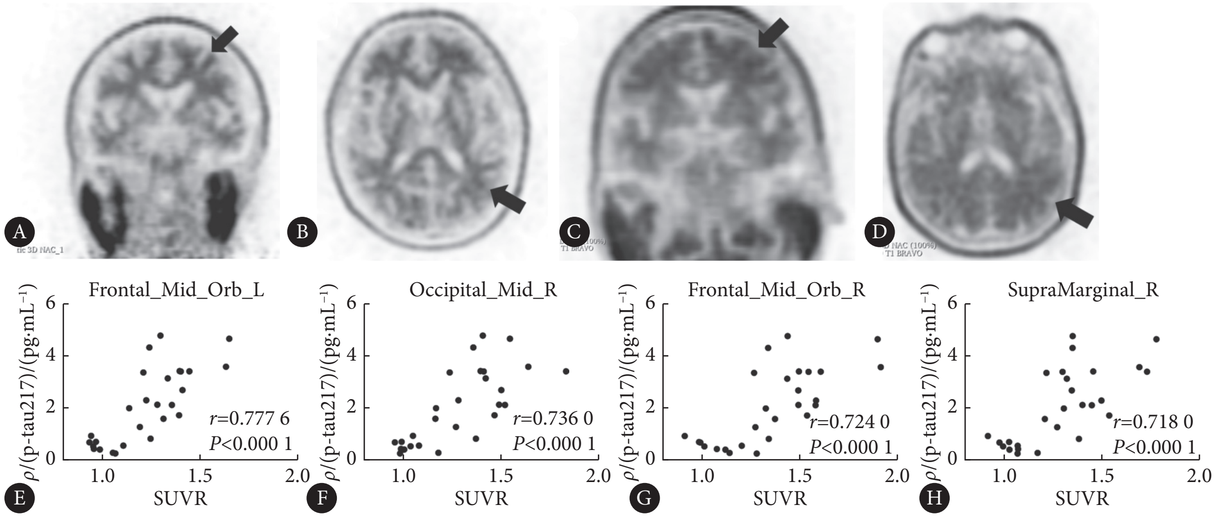

图 3 血浆标志物水平与Aβ PET摄取量相关性分析

Fig 3 Correlation analysis between plasma biomarker levels and Aβ PET uptake

A-D show the Aβ PET images of HC and AD dementia patients, with the arrows pointed at: (A) a clear radial sign in HC due to the high white matter uptake portion of the white matter not being wrapped up by the low uptake portion of the peripheral grey matter, (B) a gradient sign in HC due to the difference in uptake by grey and white matters, (C) a full sign in AD dementia patients due to the high white matter uptake portion of the brain gyrus being wrapped by the high uptake portion of the peripheral grey matter, and (D) the homogeneous sign in AD dementia patients due to the disappearance of grey-white matter uptake differences. E-H show that the Aβ PET standardized uptake value ratio (SUVR) of middle frontal gyrus, orbital part (left), middle occipital gyrus (right), middle frontal gyrus, orbital part (right), and supramarginal gyrus (right) were significantly correlated with plasma levels of p-tau217.

p-tau217、p-tau181、GFAP、NfL等检测分析，发现AD痴呆患者与HC及MCI患者的差异显著。从这几个指标综合对比来看，血浆p-tau217的诊断效果最好，区分AD痴呆患者与HC的AUC达0.96，与既往研究报道一致[24, 27-29]，说明该指标有极高的临床诊断价值。本研究又单独将各指标跟Aβ PET结果进行比较，p-tau217的结果仍然表现出最优异的准确性，AUC可达0.99，与国内外文献一致[30-32]。本研究进一步发现了血浆p-tau217水平与Aβ PET的SURV值呈正相关，尤其是额、颞、枕区的摄取量相关性最强，说明p-tau217是目前可以辅助AD病理诊断最佳的血浆标志物。

然而，本研究中MCI患者血浆标志物水平未发生显著变化，且区分MCI患者和认知正常人群的效果不佳。对比其他研究发现，在未考虑Aβ病理改变时，WU等[11]对上海地区人群的研究结果显示，血浆p-tau181及NfL水平用于区分MCI与认知正常人群的AUC分别为0.70和0.59。GONZALES等[12]对美国德克萨斯州白人的研究发现，血浆GFAP和NfL水平区分MCI和认知正常人群的AUC均为0.65。SIMRÉN等[8]对欧洲人群的研究结果显示，血浆p-tau181、NfL及GFAP区分MCI和认知正常人群的AUC分别为0.71、0.68和0.52。而本研究中血浆p-tau181、NfL及GFAP区分MCI和认知正常人群的AUC为0.53、0.63及0.58，与既往研究结果较为一致。上述结果表明，在未考虑Aβ病理改变时，血浆标志物对不同地域和种族人群MCI的区分效果均不显著。

而考虑Aβ病理改变时，CHATTERJEE等[33]对澳大利亚人群的研究结果显示，Aβ PET阳性MCI患者血浆p-tau181、NfL及GFAP水平显著高于Aβ PET阴性MCI患者，上述指标区分Aβ PET阳性和阴性MCI患者的AUC分别为0.90、0.65及0.73。该研究MCI患者中Aβ PET阳性患者占比55.9%（33/59）。另一项对爱尔兰人群的研究[15]发现，脑脊液Aβ阳性MCI患者血浆p-tau217水平显著高于脑脊液Aβ阴性MCI患者。同样，该研究中Aβ阳性患者占比达到51.5%（35/68）。而本研究接受了Aβ PET检查的MCI患者中，Aβ阳性患者仅33.3%（2/6）。上述研究结果表明，对于MCI患者而言，目前的血浆生物标志物水平与Aβ病理改变有较强的相关性。本研究与其他地域和种族的研究结果较为一致的是，在未进行Aβ病理检查时，这些血浆标志物对于MCI的诊断效果较差，这可能与四川德阳地区MCI患者Aβ PET阳性率较低、样本量过小有关，因此需要开发新的方法对MCI人群进行早期筛查。

综上所述，本研究采用国产自主研发的超灵敏数字免疫芯片技术对四川德阳地区人群进行了血浆AD痴呆标志物的检测，发现血浆p-tau217具有最佳的AD痴呆诊断价值。该检测方法成本远低于国外试剂盒，适用于大规模人群的早期筛查。本研究也存在一定的局限性：从基线结果来看，至少年龄和认知功能息息相关，因此年龄很可能是一个重要的混杂因素，解读此研究结果时应予

以考虑。此外，即对于血浆标志物的检测仅在四川地区少数人群中开展，不具有广泛代表性，未来还需要全国多中心大样本的前瞻性临床研究来验证本研究的结果。

* * *

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