

神经退行性疾病患者血清神经丝轻链蛋白水平变化的Meta分析



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【摘要】目的 系统评价血清神经丝轻链蛋白(neurofilament light chain protein, NfL)在神经退行性疾病及不同认知损害程度患者中的变化。方法 计算机检索PubMed、Embase、Web of Science、中国知网、万方和中国生物医学文献库数据库,纳入阿尔茨海默病(Alzheimer's disease, AD)、帕金森病(Parkinson's disease, PD)、多系统萎缩(multiple system atrophy, MSA)、进行性核上性麻痹(progressive supranuclear palsy, PSP)患者和健康对照均有血清NfL值的队列或病例对照研究,检索时间为建库至2023年4月30日。使用纽卡斯尔-渥太华量表评价纳入研究的风险偏倚,采用RevMan 5.4软件统计分析暴露组与非暴露组间的血清NfL值差异,合并效应量采用标准均数差(standard mean difference, SMD)及95%可信区间(confidence interval, CI)表示。结果 纳入43篇文献,共提取了62项对比研究。对PD、AD、MSA、PSP与各自健康对照分组比较,四组分别纳入9项、24项、9项、8项研究。PD组[SMD=0.27, 95%CI(0.17, 0.36)],AD组[SMD=0.97, 95%CI(0.70, 1.23)],MSA组[SMD=1.51, 95%CI(0.97, 2.05)],PSP组[SMD=1.54, 95%CI(1.14, 1.93)]血清NfL水平均高于各自健康对照组。对帕金森病认知正常(PD normal cognitive, PD-NC)与帕金森病痴呆(PD with dementia, PD-D)、阿尔茨海默病轻度认知减退(AD mild cognitive impairment, AD-MCI)与阿尔茨海默病痴呆(AD with dementia, AD-D)分组比较,两对比组分别纳入3项和9项研究,PD-D患者血清NfL水平高于PD-NC患者[SMD=0.92, 95%CI(0.63, 1.20)],AD-D患者血清NfL水平高于AD-MCI患者[SMD=0.61, 95%CI(0.49, 0.72)]。结论 PD、AD、MSA、PSP患者血清NfL水平较健康人群升高,且认知损害程度越大,血清NfL水平越高,血清NfL可能是神经退行性疾病潜在的外周生物标志物,能够进一步反映认知水平的下降。

【关键词】生物标志物;神经丝轻链蛋白;神经退行性疾病;阿尔茨海默病;帕金森病;进行性核上性麻痹;多系统萎缩;系统评价;Meta分析

Changes in serum neurofilament light chain protein levels in patients with neurodegenerative diseases: a Meta-analysis

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【Abstract】Objective To systematic evaluate the change of serum neurofilament light chain protein (NfL) level in patients with different neurodegenerative disease and different degrees of cognitive impairment. **Methods** A comprehensive search of literatures was conducted in the PubMed, Embase, Web of Science, CNKI, Wanfang and CBM from inception to April 30, 2023. Literatures with serum NfL levels in patients with Alzheimer's disease (AD), Parkinson's disease (PD), multiple system atrophy (MSA), progressive supranuclear palsy (PSP) and healthy controls were included in the cohort or case-control studies. The Newcastle-Ottawa Scale was used to evaluate the quality of the included studies. RevMan 5.4 software was used to analyze the change of serum NfL between exposure group and non-exposure group. The effect size was expressed by standard mean difference (SMD) and 95% confidence interval (CI). **Results** 62 comparative studies extracted from a total of 43 literatures were included. Comparing PD, AD, MSA, PSP with their respective healthy control groups, the four groups included 9, 24, 9, and 8 studies, respectively. The levels of serum NfL in the PD group [SMD=0.27, 95%CI (0.17, 0.36)], AD group [SMD=0.97, 95%CI (0.70, 1.23)], MSA group [SMD=1.51, 95%CI (0.97, 2.05)], and PSP group [SMD=1.54 95%CI (1.14, 1.93)] were higher than those in the healthy controls in their respective groups. Further comparison was conducted between PD normal cognitive (PD-NC) and PD with dementia (PD-D), AD mild cognitive impairment (AD-MCI) and AD with dementia (AD-D) groups. 3 and 9 studies were included in the two comparison groups, respectively. The serum NfL levels of PD-D patients were higher than those of PD-NC patients [SMD=0.92, 95%CI (0.63, 1.20)], and the serum NfL levels of AD-D patients were higher than those of AD-MCI patients [SMD=0.61, 95%CI (0.49, 0.72)]. **Conclusion** The serum NfL levels in patients with PD, AD, MSA, and PSP are higher than those in healthy individuals, and the greater the degree of cognitive impairment, the higher the serum NfL levels. Serum NfL may be a potential peripheral biomarker reflecting neurodegenerative diseases, which can further reflect the decline in cognitive levels.

【Keywords】 Biomarkers; Neurofilament light chain protein; Neurodegenerative disease; Alzheimer's disease; Parkinson's disease; Progressive supranuclear palsy; Multiple system atrophy; Systematic review; Meta-analysis

神经退行性疾病是一组慢性进行性、系统性、原因不明的疾病，随着疾病的发展，患者通常会逐渐出现认知功能下降、行为控制能力减弱、运动能力丧失等症状，不仅对患者的生活质量造成严重影响，还会对社会医疗体系带来巨大压力，积极寻找疾病的生物标志物将有助于对这类疾病进行早期诊断、治疗效果预测，以及疾病进展监测等^[1-2]。神经丝轻链蛋白（neurofilament light chain protein, NfL）是神经丝的一个亚基，被认为是维持轴突稳定和促进轴突生长的主要结构。研究发现脑脊液或血液中 NfL 升高是神经元 / 轴突损伤和退行性病变的一个指标^[3]，进一步的研究还发现更高水平的 NfL 与更快的疾病进展和更高的脑萎缩率有关^[4-5]。系统评价发现，与健康

对照组相比，阿尔茨海默病（Alzheimer's disease, AD）、额颞叶痴呆、路易体痴呆患者脑脊液 NfL 水平显著增高，但帕金森病（Parkinson's disease, PD）患者和对照组之间脑脊液 NfL 水平差异无统计学意义^[6]。现有系统评价多纳入脑脊液 NfL 相关研究，纳入血液 NfL 相关研究的较少，另外神经退行性疾病往往伴随认知损害，比如 PD 的白质轴突变性导致脑白质受损，而认知功能障碍又多见于中重度脑白质疏松患者^[7]。但目前尚无评估血清 NfL 在反映认知损害方面作用的 Meta 分析。故本研究对神经退行性疾病患者与健康对照组以及不同认知损害水平患者的血清 NfL 水平差异进行 Meta 分析，以明确其在监测神经退行性疾病发生发展中的临床价值。

1 资料与方法

1.1 纳入与排除标准

纳入标准：①研究类型：队列研究或病例对照研究，如果存在前瞻性研究，则选取研究的基线数据；②研究对象：诊断符合 AD、PD、多系统萎缩（multiple system atrophy, MSA）、进行性核上性麻痹（progressive supranuclear palsy, PSP）疾病诊断标准。其中帕金森病痴呆（PD with dementia, PD-D）、阿尔茨海默病轻度认知功能障碍（AD mild cognitive impairment, AD-MCI）患者为在符合 PD、AD 相关诊断标准的基础上，通过简易精神状态检查量表（Mini Mental Status Examination, MMSE）、蒙特利尔认知评估量表（Montreal Cognitive Assessment, MoCA）以及日常生活损害等临床诊断标准诊断的不同认知损害水平的患者；③暴露组与非暴露组：PD、AD、MSA、PSP 与健康人群血清 NfL 水平对比时，患病人群为暴露组，健康对照人群为非暴露组；帕金森病认知正常（PD normal cognitive, PD-NC）与 PD-D 组、AD-MCI 与阿尔茨海默病痴呆（AD with dementia, AD-D）组血清 NfL 水平对比时，暴露组分别为 PD-D、AD-D 患者，非暴露组分别为 PD-NC、AD-MCI 患者；④结局指标：血清 NfL 水平，其检测技术限定为 Simoa 平台技术。

排除标准：①缺乏健康对照组；②未使用定量方法确定暴露组和非暴露组的结果数值；③原始数据为二次加工过的文献，如进行对数换算等；④非暴露组患有会混淆研究结果的其他神经、精神或身体疾病；⑤非人类研究；⑥评论、信函、案例报告、方案、编辑、评论、会议摘要等类型文献。

1.2 文献检索策略

计算机检索 PubMed、Embase、Web of Science、中国知网、万方和中国生物医学文献库等数据库，检索时限为建库至 2023 年 4 月 30 日。检索字段采用“主题词 + 自由词”的形式，并通过交叉核对引用的参考文献，以获得更多符合条件的研究。英文检索词包括：NFL、serum NfL、neurofilament light、multiple system atrophy、Parkinson's disease、Alzheimer's disease、progressive supranuclear palsy；中文检索词包括：帕金森病、老年人帕金森病、遗传性帕金森病、

阿尔茨海默病、痴呆症、认知功能障碍、多系统萎缩、多系统脑萎缩、多发性系统萎缩、进行性核上性麻痹、核上性麻痹、进行性核上性眼肌麻痹、神经丝轻链蛋白。PubMed 检索策略如框 1 所示。

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#1 "NFL"[Title/Abstract] OR "serum NfL"[Title/Abstract] OR
  "neurofilament light"[Title/Abstract]
#2 "Parkinson disease" [Mesh]
#3 "PD"[Title/Abstract] OR "Parkinson's Disease"[Title/
  Abstract] OR "Idiopathic Parkinson's Disease"[Title/
  Abstract] OR "Lewy Body Parkinson's Disease"[Title/
  Abstract] OR "Primary Parkinsonism"[Title/Abstract]
#4 "Alzheimer disease" [Mesh]
#5 "AD"[Title/Abstract] OR "Alzheimer Dementia"[Title/
  Abstract] OR "Alzheimer's Disease"[Title/Abstract] OR
  "Alzheimer Type Dementia"[Title/Abstract] OR "Alzheimer
  Syndrome"[Title/Abstract]
#6 "Multiple system atrophy" [Mesh]
#7 "MSA"[Title/Abstract] OR "Multisystemic Atrophy"[Title/
  Abstract] OR "Multisystemic Atrophies"[Title/Abstract] OR
  "Multisystem Atrophy"[Title/Abstract]
#8 "Progressive supranuclear palsy" [Mesh]
#9 "PSP"[Title/Abstract] OR "Supranuclear Palsies"[Title/
  Abstract] OR "Richardson Syndrome"[Title/Abstract]
#10 #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
#11 #1 AND #10
```

框1 PubMed检索策略

Box 1. Search strategy in PubMed

1.3 文献筛选与资料提取

由两位研究者按照纳入排除标准独立进行文献筛选与资料提取，并进行交叉核对，如遇分歧则通过讨论或与第三位研究者协商确定，提取的资料包括：作者、出版年份、年龄、地区、血清 NfL 测量方法、MMSE 或 MoCA 认知评估量表评分，以及暴露组和非暴露组血清 NfL 的平均值和标准差。若原始研究的数据不符合“均数 ± 标准差”的要求，则参考 Luo^[8] 和 Wan^[9] 等的统计学方法进行转化。

1.4 纳入文献的偏倚风险评价

由两位研究者根据纽卡斯尔-渥太华量表（the Newcastle-Ottawa Scale, NOS）标准^[10]独立评价纳入文献的偏倚风险。NOS 量表包含三大领

域（研究人群选择、可比性、暴露 / 结果评价），共八个条目，除可比性条目最高可评 2 分外，其余条目最高可评 1 分，满分为 9 分，评分 > 7 分为高质量研究，评分 < 6 分为低质量研究，反之为中等质量研究。如有不一致则通过讨论或与第三位研究者协商确定。

1.5 统计学分析

血清 NFL 数据为连续性变量，为消除不同研究间数据单位不一致的影响，采用标准化均数差（standard mean difference, SMD）作为合并效应量。采用 RevMan 5.4 软件统计分析暴露组和非暴露组之间的血清 NFL 值差异。采用 Q 检验和 I^2 检验进行异质性分析，若 $P > 0.1$ 且 $I^2 \leq 50\%$ ，认为研究间存在异质性的可能性小，选用固定效应模型进行 Meta 分析；若 $P \leq 0.1$ 且 $I^2 > 50\%$ ，认为研究间存在异质性的可能性大，选用随机效应模型进行 Meta 分析，并进一步以地区进行分组探讨异质性来源。敏感性分析采用逐步剔除文献法。若纳入研究数超过 10 项，通过绘制漏斗图评估发表偏倚。

2 结果

2.1 文献筛选流程及结果

初步检索获得相关文献 2 072 篇，剔除重复文献后获得文献 859 篇，通过阅读文题和摘要初筛后获得文献 123 篇，根据纳入排除标准进一步筛选后，最终纳入 Meta 分析文献 43 篇，见图 1。

2.2 纳入研究的基本特征与偏倚风险评价

由于部分文献同时报道了多组对比研究，故纳入的 43 篇文献共提取了 62 项对比研究。其中，PD、AD、MSA、PSP 与各自健康对照组的分组比较分别纳入 9 项、24 项、9 项、8 项研究，PD-NC 与 PD-D 的分组比较纳入 3 项研究，AD-MCI 与 AD-D 的分组比较纳入 9 项研究，见表 1。发表年份主要集中在 2019—2023 年间，研究人群年龄段主要为 60~70 岁，涵盖北美、亚洲、欧洲等地区。NOS 评估结果显示高质量研究 9 项、中等质量研究 53 项，无低质量研究，见表 1。

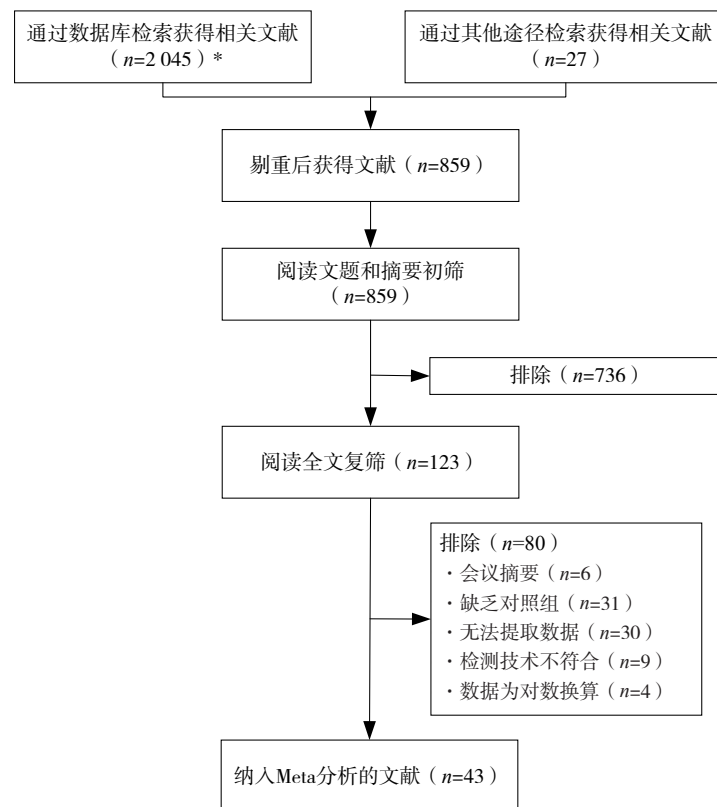


图1 文献筛选流程及结果

Figure 1. Flow chart and results of literature search

注：*检索的数据库及检出文献数具体为PubMed (n=856)、Web of Science (n=654)、Embase (n=465)、中国知网 (n=19)、万方 (n=30)、中国生物医学文献数据库 (n=21)。

表1 纳入研究的一般特征和偏倚风险评估结果 ($\bar{x} \pm SD$)
 Table 1. Basic characteristics and risk of bias assessment of included studies ($\bar{x} \pm SD$)

研究	国家	疾病比较组	暴露组			非暴露组			NOS 评分		
			人数	年龄 (岁)	MMSE/MoCA 评分	NfL (pg · mL ⁻¹)	人数	年龄 (岁)		MMSE/MoCA 评分	NfL (pg · mL ⁻¹)
Sampedro 2020 ^[11]	西班牙	PD vs. 健康对照	56	61.70 ± 10.10	—	10.47 ± 3.60	133	62.30 ± 9.70	—	12.28 ± 5.60	7
Aamodt 2021 ^[12]	美国	PD vs. 健康对照	198	69.35 ± 6.72	—	15.77 ± 6.50	139	66.35 ± 8.24	—	16.44 ± 7.94	7
Pagonabarraga 2022 ^[13]	西班牙	PD vs. 健康对照	40	66.00 ± 7.00	—	10.90 ± 5.00	109	65.30 ± 7.00	—	13.80 ± 5.00	7
Mao 2023 ^[14]	中国	PD vs. 健康对照	37	62.20 ± 6.20	—	8.50 ± 4.70	103	63.50 ± 8.70	—	13.70 ± 9.00	7
Ma 2021 ^[15]	中国	PD vs. 健康对照	144	61.53 ± 10.91	—	11.71 ± 5.78	301	62.11 ± 9.77	—	13.00 ± 6.53	8
Zhu 2021 ^[16]	中国	PD vs. 健康对照	38	64.90 ± 10.60	28.80 ± 0.90	16.50 ± 7.30	130	65.10 ± 10.20	24.40 ± 5.40	24.30 ± 16.10	7
Nabizadeh 2023 ^[17]	伊朗	PD vs. 健康对照	176	61.50 ± 10.90	—	11.89 ± 6.71	228	63.10 ± 9.20	—	13.74 ± 6.71	7
Yin 2022 ^[18]	中国	PD vs. 健康对照	38	64.90 ± 10.60	—	16.50 ± 7.30	24	61.10 ± 11.10	—	16.20 ± 5.90	7
Imariso 2021 ^[19]	瑞士	PD vs. 健康对照	69	71.70 ± 7.10	—	25.70 ± 10.60	71	65.10 ± 10.50	27.60 ± 2.50	27.70 ± 16.30	7
Brickman 2021 ^[20]	美国	AD vs. 健康对照	169	81.01 ± 6.31	—	31.10 ± 28.96	131	82.99 ± 6.49	—	36.55 ± 24.63	7
Benedet 2021 ^{[21]*}	加拿大	AD vs. 健康对照	114	69.90 ± 9.40	29.00 ± 1.00	22.10 ± 9.80	45	66.10 ± 9.70	19.00 ± 6.00	33.60 ± 13.50	7
Benedet 2021 ^{[21]*}	法国	AD vs. 健康对照	21	64.40 ± 9.50	27.40 ± 2.50	13.10 ± 6.80	76	72.20 ± 8.40	19.30 ± 5.60	24.40 ± 8.70	8
Smirnov 2022 ^[22]	美国	AD vs. 健康对照	29	83.60 ± 6.90	27.90 ± 2.10	32.30 ± 13.80	124	74.80 ± 9.40	21.90 ± 6.10	39.30 ± 24.50	9
Palmqvist 2020 ^{[23]w}	美国	AD vs. 健康对照	47	83.64 ± 9.94	26.64 ± 3.82	31.85 ± 19.04	34	84.11 ± 7.97	20.96 ± 6.42	30.19 ± 11.22	7
Palmqvist 2020 ^{[23]w}	瑞典	AD vs. 健康对照	301	65.96 ± 15.49	29.00 ± 1.48	13.35 ± 6.55	121	74.23 ± 5.78	20.35 ± 3.75	23.19 ± 11.10	7
Stevenson-Hoare 2023 ^[24]	英国	AD vs. 健康对照	508	82.20 ± 6.72	—	32.90 ± 13.70	1 439	68.10 ± 8.03	—	31.00 ± 13.90	6
Illán-Gala 2021 ^[25]	美国	AD vs. 健康对照	55	52.20 ± 13.00	28.90 ± 1.00	11.45 ± 5.33	43	65.20 ± 10.00	21.50 ± 6.00	27.56 ± 11.81	7
Chouliaras 2022 ^[26]	英国	AD vs. 健康对照	73	70.20 ± 7.79	—	20.90 ± 18.60	63	73.90 ± 7.80	—	28.20 ± 16.80	7
Planche 2023 ^[27]	法国	AD vs. 健康对照	2 020	70.98 ± 8.61	28.29 ± 1.48	18.33 ± 8.31	257	75.56 ± 8.05	26.35 ± 2.24	23.67 ± 9.24	7
Baiardi 2022 ^[28]	意大利	AD vs. 健康对照	60	61.70 ± 4.90	—	11.12 ± 4.63	97	67.80 ± 9.30	21.90 ± 6.20	22.28 ± 8.20	8
Palmqvist 2019 ^[29]	瑞典	AD vs. 健康对照	366	72.00 ± 5.00	28.90 ± 1.10	21.00 ± 11.80	64	76.00 ± 5.00	21.80 ± 3.70	43.80 ± 28.70	6
Chatterjee 2023 ^[30]	澳大利亚	AD vs. 健康对照	81	73.74 ± 5.96	29.04 ± 1.03	22.46 ± 11.62	46	75.17 ± 7.20	20.41 ± 4.87	32.58 ± 16.66	7
Benussi 2022 ^[31]	意大利	AD vs. 健康对照	27	51.57 ± 23.48	29.64 ± 0.78	7.98 ± 5.63	48	67.72 ± 8.56	24.50 ± 3.82	20.56 ± 9.55	8
Sugarman 2020 ^[32]	美国	AD vs. 健康对照	238	72.38 ± 7.69	29.39 ± 0.91	15.33 ± 10.47	156	76.74 ± 8.12	21.11 ± 6.17	26.49 ± 17.30	7
Lewczuk 2018 ^[33]	德国	AD vs. 健康对照	41	52.50 ± 13.10	29.30 ± 0.90	22.00 ± 12.40	33	70.80 ± 7.60	21.20 ± 3.40	49.10 ± 28.40	6

续表1

研究	国家	疾病比较组	暴露组				非暴露组				NOS 评分
			人数	年龄 (岁)	MMSE/MoCA 评分	NfL (pg · mL ⁻¹)	人数	年龄 (岁)	MMSE/MoCA 评分	NfL (pg · mL ⁻¹)	
Barker 2021 ^[34]	美国	AD vs. 健康对照	51	70.80 ± 5.90	29.40 ± 0.80	14.20 ± 6.10	156	74.80 ± 8.20	25.30 ± 4.30	21.90 ± 13.10	9
Subramanian 2021 ^[35]	印度	AD vs. 健康对照	24	64.25 ± 9.03	—	31.99 ± 10.84	48	67.71 ± 8.24	—	70.09 ± 33.77	6
Halbgebauer 2022 ^[36]	德国	AD vs. 健康对照	77	60.00 ± 19.00	—	20.35 ± 11.33	20	69.00 ± 8.00	—	29.00 ± 9.57	7
Alcolea 2021 ^[37]	西班牙	AD vs. 健康对照	46	54.80 ± 12.30	29.10 ± 1.10	8.90 ± 5.00	8	72.30 ± 5.00	23.60 ± 3.20	16.50 ± 6.60	7
Steinacker 2018 ^[38]	德国	AD vs. 健康对照	15	64.80 ± 11.30	29.00 ± 0.80	21.70 ± 20.60	26	67.00 ± 8.10	21.60 ± 6.00	32.30 ± 15.80	7
Silva-Spinola 2022 ^[39]	葡萄牙	AD vs. 健康对照	37	60.10 ± 4.20	—	8.90 ± 2.70	37	61.10 ± 5.00	—	19.00 ± 7.60	7
Santo 2023 ^[40]	西班牙	AD vs. 健康对照	36	61.70 ± 8.20	28.80 ± 1.10	9.20 ± 3.90	54	66.90 ± 7.90	20.40 ± 4.60	15.60 ± 5.70	7
Bolsewig 2022 ^[41]	意大利	AD vs. 健康对照	29	68.00 ± 4.68	28.00 ± 1.56	11.71 ± 4.67	47	72.29 ± 6.12	22.71 ± 4.59	20.29 ± 4.58	8
Huang 2023 ^[42]	中国	MSA vs. 健康对照	85	61.90 ± 8.27	28.00 ± 2.07	15.10 ± 8.94	15	58.60 ± 6.05	22.30 ± 7.13	32.60 ± 15.00	6
Li 2022 ^[43]	中国	MSA vs. 健康对照	33	66.15 ± 4.75	—	16.00 ± 5.18	13	63.11 ± 7.69	26.69 ± 2.10	86.53 ± 33.74	7
Marques 2019 ^[44]	荷兰	MSA vs. 健康对照	53	57.50 ± 9.80	—	11.50 ± 6.50	22	60.70 ± 7.10	28.00 ± 2.20	22.20 ± 11.00	7
Quadalti 2021 ^[45]	意大利	MSA vs. 健康对照	37	58.10 ± 10.10	—	9.15 ± 4.55	54	61.10 ± 8.00	28.10 ± 2.00	33.04 ± 12.41	7
Zhang 2022 ^[46]	中国	MSA vs. 健康对照	60	59.07 ± 3.80	—	12.07 ± 5.88	91	59.01 ± 7.29	—	33.28 ± 14.07	8
Wilke 2018 ^[47]	德国	MSA vs. 健康对照	25	64.45 ± 11.48	—	34.81 ± 12.81	25	64.09 ± 12.18	—	66.82 ± 38.91	7
Guo 2023 ^[48]	中国	MSA vs. 健康对照	100	59.50 ± 8.91	—	13.74 ± 8.53	73	58.62 ± 7.85	—	40.92 ± 44.89	7
Peng 2023 ^[49]	中国	MSA vs. 健康对照	211	57.21 ± 9.06	—	39.84 ± 75.29	214	58.29 ± 6.71	24.97 ± 4.10	73.42 ± 122.93	7
Shen 2023 ^[50]	中国	MSA vs. 健康对照	74	55.00 ± 7.80	28.20 ± 2.20	11.40 ± 6.62	56	57.00 ± 12.30	24.60 ± 4.10	42.20 ± 50.00	6
Rojas 2016 ^[51]	美国	PSP vs. 健康对照	12	70.00 ± 8.00	29.40 ± 0.70	17.50 ± 5.00	15	66.40 ± 6.00	27.30 ± 1.00	31.00 ± 17.00	7
Donker 2018 ^[52]	荷兰	PSP vs. 健康对照	95	68.50 ± 6.30	—	30.60 ± 15.81	131	71.30 ± 7.70	23.90 ± 4.60	64.23 ± 32.76	6
Huang 2023 ^[42]	中国	PSP vs. 健康对照	85	61.90 ± 8.27	28.00 ± 2.07	15.10 ± 8.94	85	66.00 ± 7.07	20.00 ± 6.75	40.90 ± 22.30	6
Li 2022 ^[43]	中国	PSP vs. 健康对照	33	66.15 ± 4.75	—	16.00 ± 5.18	8	70.00 ± 7.31	25.00 ± 5.34	53.90 ± 22.97	6
Marques 2019 ^[44]	荷兰	PSP vs. 健康对照	53	57.50 ± 9.80	—	11.50 ± 6.50	7	68.90 ± 4.10	25.40 ± 2.80	25.60 ± 8.40	7
Quadalti 2021 ^[45]	意大利	PSP vs. 健康对照	37	58.10 ± 10.10	—	9.15 ± 4.55	40	71.20 ± 6.80	25.10 ± 5.40	29.08 ± 16.45	7
Chouliaras 2022 ^[26]	英国	PSP vs. 健康对照	73	70.20 ± 7.79	—	20.90 ± 18.60	19	69.00 ± 5.91	—	31.10 ± 15.00	9
Baiardi 2022 ^[28]	意大利	PSP vs. 健康对照	60	61.70 ± 4.90	—	11.12 ± 4.63	31	69.20 ± 10.2	25.40 ± 5.10	27.06 ± 13.60	7
Mao 2023 ^[14]	中国	PD-NC vs. PD-D	36	59.00 ± 9.30	26.00 ± 4.00 [†]	11.10 ± 8.70	30	69.20 ± 5.50	10.00 ± 8.00 [†]	20.80 ± 16.70	7
Zhu 2021 ^[16]	中国	PD-NC vs. PD-D	57	62.80 ± 10.50	28.40 ± 1.70	17.90 ± 8.90	39	68.70 ± 8.60	18.10 ± 4.90	35.70 ± 21.70	7
Lin 2018 ^[53]	中国	PD-NC vs. PD-D	26	69.60 ± 10.80	26.90 ± 2.60	15.40 ± 9.90	23	76.30 ± 9.10	23.30 ± 4.60	23.30 ± 10.80	7

续表1

研究	国家	疾病比较组	暴露组			非暴露组			NOS 评分		
			人数	年龄(岁)	MMSE/MoCA 评分	NfL (pg·mL ⁻¹)	人数	年龄(岁)		MMSE/MoCA 评分	NfL (pg·mL ⁻¹)
Benedet 2021 ^[21]	加拿大	AD-MCI vs. AD-D	39	71.20 ± 7.70	28.00 ± 2.00	25.70 ± 14.40	45	66.10 ± 9.70	19.00 ± 6.00	33.60 ± 13.50	7
Palmqvist 2020 ^[23]	瑞典	AD-MCI vs. AD-D	178	71.08 ± 7.92	27.00 ± 2.98	16.79 ± 8.15	121	74.23 ± 5.78	20.35 ± 3.75	23.19 ± 11.10	7
Palmqvist 2019 ^[29]	瑞典	AD-MCI vs. AD-D	157	72.00 ± 5.00	26.70 ± 1.80	29.00 ± 17.90	64	76.00 ± 5.00	21.80 ± 3.70	43.80 ± 28.70	6
Chatterjee 2023 ^[30]	澳大利亚	AD-MCI vs. AD-D	33	75.61 ± 5.66	27.58 ± 1.48	28.56 ± 17.80	46	75.17 ± 7.20	20.41 ± 4.87	32.58 ± 16.66	7
Sugarman 2020 ^[32]	美国	AD-MCI vs. AD-D	185	74.99 ± 7.24	28.20 ± 1.67	17.77 ± 10.25	156	76.74 ± 8.12	21.11 ± 6.17	26.49 ± 17.30	7
Lewczuk 2018 ^[33]	美国	AD-MCI vs. AD-D	25	71.30 ± 8.40	26.70 ± 2.10	38.10 ± 15.90	33	70.80 ± 7.60	21.20 ± 3.40	49.10 ± 28.40	6
Alcolea 2021 ^[37]	西班牙	AD-MCI vs. AD-D	46	72.60 ± 6.50	25.80 ± 2.70	16.80 ± 9.30	8	72.30 ± 5.00	23.60 ± 3.20	16.50 ± 6.60	7
Steinacker 2018 ^[38]	德国	AD-MCI vs. AD-D	17	63.10 ± 9.30	27.90 ± 1.90	16.60 ± 8.10	26	67.00 ± 8.10	21.60 ± 6.00	32.30 ± 15.80	7
Sarto 2023 ^[40]	西班牙	AD-MCI vs. AD-D	183	69.20 ± 7.60	25.00 ± 3.40	12.10 ± 5.70	54	66.90 ± 7.90	20.40 ± 4.60	15.60 ± 5.70	7

注：*表示同一篇文章中报道的同一疾病在不同研究地区的两项对比研究；*表示结果为MoCA认知量表得分；AD：阿尔茨海默病；AD-D：阿尔茨海默病痴呆；AD-MCI：阿尔茨海默病轻度认知功能障碍；PD：帕金森病；PD-D：帕金森病痴呆；PD-NC：帕金森病非痴呆；PSP：进行性核上性麻痹；MMSE：简易精神状态检查量表；MoCA：蒙特利尔认知评估量表；-：未报告。

2.3 Meta分析结果

2.3.1 帕金森病

9项研究^[11-19]比较了健康者与PD患者的血清NfL水平，研究间异质性较小($I^2=38%$, $P=0.11$)，基于固定效应模型的Meta分析结果显示，PD患者血清NfL水平高于健康对照组，差异具有统计学意义[SMD=0.27, 95%CI (0.17, 0.36), $P < 0.001$]，见图2。

3项研究^[14, 16, 53]比较了PD-NC患者与PD-D患者的血清NfL水平，研究间异质性较小($I^2=0%$, $P=0.40$)，基于固定效应模型的Meta分析结果显示，PD-D患者血清NfL水平高于PD-NC患者，差异具有统计学意义[SMD=0.92, 95%CI (0.63, 1.20), $P < 0.001$]，见图3。

2.3.2 阿尔兹海默病

来源于22篇文献^[20-41]的24项研究比较了健康者与AD患者的血清NfL水平，研究间异质性较大($I^2=95%$, $P < 0.001$)，基于随机效应模型的Meta分析结果显示，AD患者血清NfL水平高于健康对照组，差异具有统计学意义[SMD=0.97, 95%CI (0.70, 1.23), $P < 0.001$]，见图4。根据研究地区进行亚组分析，北美、欧洲地区AD患者血清NfL水平均高于健康对照组，差异具有统计学意义，见表2。

9项研究^[21, 23, 29-30, 32-33, 37-38, 40]比较了AD-MCI患者与AD-D患者的血清NfL水平，研究间异质性较小($I^2=12%$, $P=0.34$)，基于固定效应模型的Meta分析结果显示，AD-D患者血清NfL水平高于AD-MCI患者，差异具有统计学意义[SMD=0.61, 95%CI (0.49, 0.72), $P < 0.001$]，见图5。

2.3.3 多系统萎缩

9项研究^[42-50]比较了健康者与MSA患者的血清NfL水平，研究间异质性较大($I^2=94%$, $P < 0.001$)，基于随机效应模型的Meta分析结果显示，MSA患者血清NfL水平高于健康者，差异具有统计学意义[SMD=1.51, 95%CI (0.97, 2.05), $P < 0.001$]，见图6。根据研究地区进行亚组分析，亚洲、欧洲地区MSA患者血清NfL水平均高于健康对照组，差异具有统计学意义，见表2。

2.3.4 进行性核上性麻痹

8项研究^[26, 28, 42-45, 51-52]比较了健康者与PSP患者的血清NfL水平，研究间异质性较大($I^2=78%$, $P < 0.001$)，基于随机效应模型的Meta分析结

果显示, PSP 患者血清 NfL 水平高于健康者, 差异具有统计学意义[SMD=1.54, 95%CI(1.14, 1.93)], $P < 0.001$], 见图 7。根据研究地区进行亚组分析, 亚洲、欧美地区 PSP 患者血清 NfL 水平均高于健

康对照组, 差异具有统计学意义, 见表 2。

2.3.5 敏感性分析与发表偏倚

采用逐步剔除文献法进行敏感性分析, 结果显示各组 Meta 分析比较得到的 SMD 值未发生明

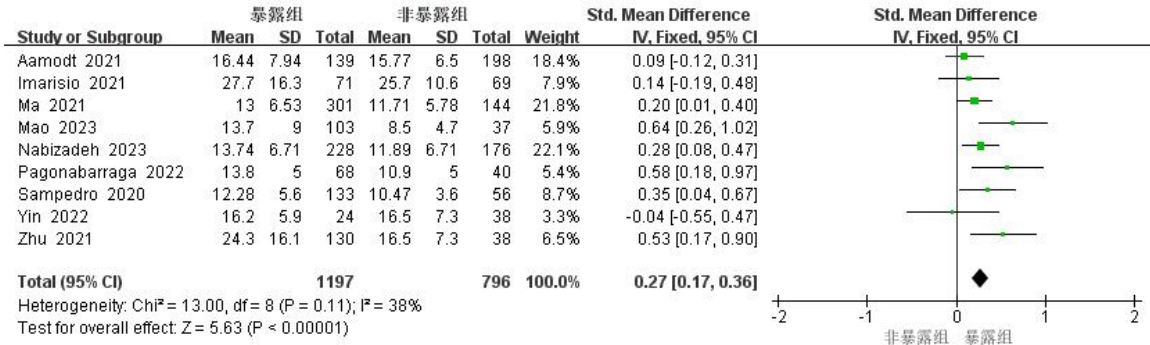


图2 PD暴露组与非暴露组血清NfL水平森林图

Figure 2. Forest plot of serum NfL levels between PD exposed and non-exposed groups

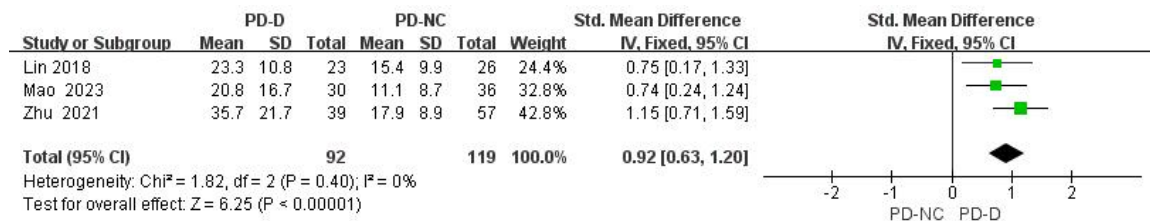


图3 PD-D组与PD-NC组血清NfL水平森林图

Figure 3. Forest plot of serum NfL levels in the PD-D and PD-NC groups

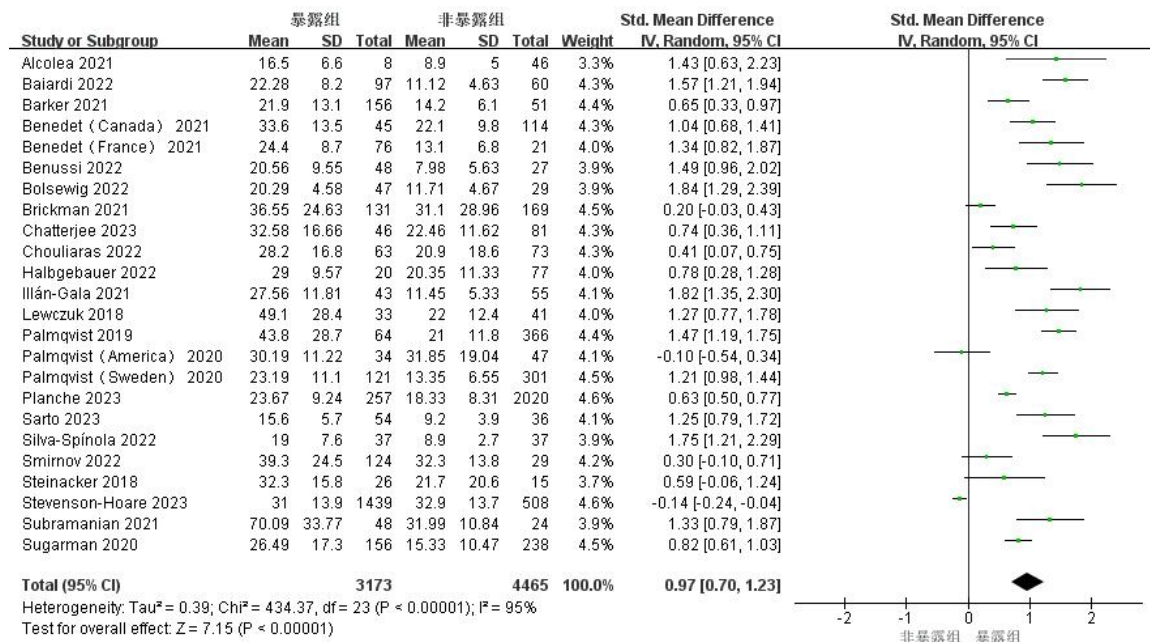


图4 AD暴露组与非暴露组血清NfL水平森林图

Figure 4. Forest plot of serum NfL levels between AD exposed and non-exposed groups

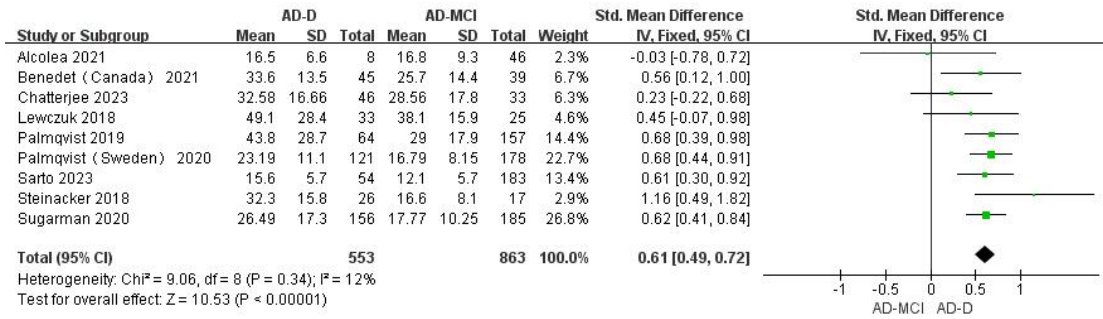


图5 AD-D组与AD-MCI组血清NfL水平森林图

Figure 5. Forest plot of serum NfL levels in the AD-D and AD-MCI groups

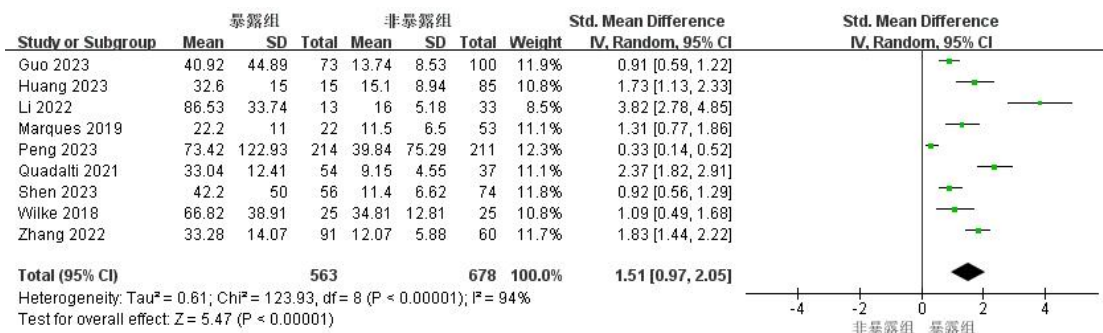


图6 MSA暴露组与非暴露组血清NfL水平森林图

Figure 6. Forest plot of serum NfL levels between MSA exposed and non-exposed groups

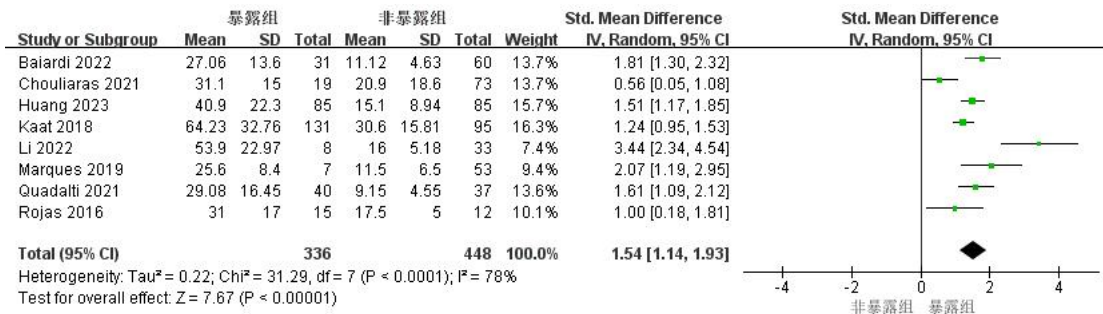


图7 PSP暴露组与非暴露组血清NfL水平森林图

Figure 7. Forest plot of serum NfL levels between PSP exposed and non-exposed groups

表2 亚组分析结果汇总表

Table 2. Summary table of subgroup analysis results

疾病	亚组	纳入研究数	异质性检验结果		效应模型	Meta分析结果		
			P值	I ² 值		SMD (95%CI)	P值	Z值
AD	北美地区	7 ^[20-23, 25, 32, 34]	<0.001	90%	随机	0.67 (0.29, 1.05)	0.006	3.44
	欧洲地区	15 ^[21, 23-24, 26-29, 31, 33, 36-41]	<0.001	96%	随机	1.11 (0.73, 1.50)	<0.001	5.68
MSA	亚洲地区	6 ^[42-43, 46, 48-50]	<0.001	95%	随机	1.47 (0.81, 2.12)	<0.001	4.38
	欧洲地区	3 ^[44-45, 47]	0.003	83%	随机	1.60 (0.82, 2.37)	<0.001	4.03
PSP	亚洲地区	2 ^[42-43]	0.001	91%	随机	2.40 (0.52, 4.29)	0.01	2.50
	欧美地区	6 ^[26, 28, 44-45, 51-52]	0.005	70%	随机	1.35 (0.95, 1.75)	<0.001	6.65

显变化,提示结果稳定可靠。健康者与 AD 患者血清 NfL 比较纳入研究数超过 10 项,对其进行发表偏倚检验,漏斗图中纳入研究左右基本对称并趋近于中线,提示存在发表偏倚的可能性较小,见图 8。其他比较组纳入研究数不足 10 项,故未行发表偏倚评估。

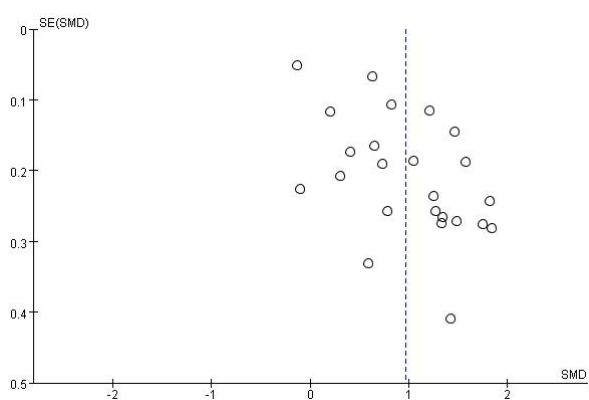


图8 AD暴露组与非暴露组发表偏倚分析漏斗图 (随机效应模型)

Figure 8. Funnel plot of publication bias analysis between AD exposed and non-exposed groups (random effects model)

3 讨论

多项研究发现 NfL 与神经退行性疾病有关。本研究结果显示 PD 患者血清 NfL 明显高于健康对照组,但有系统评价发现 PD 患者与健康对照间 NfL 水平无明显差异^[6],可能与纳入有关 PD 的研究较少,且无血清 NfL 数据有关。此外,PD 患者的病理特征为黑质多巴胺能神经元变性丢失^[54],而在早期阶段多巴胺能神经元轴突变性并不明显,可能是导致 PD 患者与健康组间 NfL 水平无差异的重要原因之一^[55]。另有研究发现 NfL 可能参与了认知功能下降的病理过程,如 Karran 等^[56]研究发现在 AD 中 NfL 与皮质变薄有关,与 β -淀粉样蛋白聚集导致神经变性的病理生理学机制是一致的,但在疾病后期的发展中两者相互独立。一项尸检研究发现 PD-D 患者海马区域老年斑存在 NfL 成分,但在认知正常的 PD 患者中无类似发现^[57]。本研究针对 PD、AD 患者间不同认知损害程度血清 NfL 水平进行了 Meta 分析,结果均显示认知损害越大,血清 NfL 水平越高,提示血清 NfL 能够有效反映脑内神经退行性病变的严重程度,并作为神经退行性疾病的外周生物标志物。

本研究限定了原始研究血清 NfL 的检测技术为 Simoa 平台技术。虽然 NfL 水平历来常使用酶联免疫吸附试验 (ELISA) 和电化学发光 (ECL) 测定技术进行测量,但已有研究发现 ELISA 定量测量血清 NfL 时灵敏度不足, ECL 的灵敏度也不足以检测血清 NfL 的最低浓度^[58]。本研究通过检索原始研究发现 2017 年以后发表的研究几乎均利用超敏感的 Simoa 平台技术^[59],故为了更好的明确血清 NfL 的价值,增加研究的可靠性,本研究限定纳入研究的血清 NfL 检测技术为 Simoa 平台技术。

目前认为血液中 NfL 是轴突膜破坏后被释放到脑脊液,进而引流进入静脉血,或通过血脑屏障扩散进入血液中。虽然已有研究证明了在大部分神经退行性疾病中脑脊液 NfL 与血清 NfL 的相关性^[60],但既往基于脑脊液 NfL 所得出的研究结论并不能简单的等同于基于血清 NfL 得到的结论。Kuhle 等^[58]明确指出脑脊液和血清 NfL 的测量值并非高度相关,不同人员的检测操作差异等也可能导致实验数据误差,因此有必要单独研究讨论血清 NfL。但是造成脑脊液与血清 NfL 间测量值不同的原因尚不完全明确,除开检测技术本身可能性外,也有学者提出是由于血清中异嗜性抗体的存在引起的基质效应导致了两者之间的不同^[61]。

NfL 作为生物标志物的研究是目前研究的热点,有学者提出 NfL 变化率比 NfL 绝对值更能有效预测神经变性和认知能力下降等方面的疾病进展。研究发现在症状发生前的 AD 中 NfL 变化率越大,个体就越容易转变为有症状的 AD,在皮质萎缩中亦有类似发现,提示血清 NfL 的纵向随访可以间接反映大脑的神经变性程度,且相对便宜,可及性高,其应用价值与神经影像学相当^[62-63]。但总体而言关于 NfL 变化率的研究较少,没有充足的研究证明证据该结论。

使用血清 NfL 作为神经退行性疾病的潜在生物标志物是可行的,但是将血清 NfL 作为神经退行性疾病之间的诊断标准还需商榷。本研究结果显示,MSA 组以及 PSP 组的 SMD 值相较于 PD 组及 AD 组更高,这表明 MSA 和 PSP 患者更容易出现血清 NfL 水平的增高。但是由于目前纳入的原始研究有限,无法得出血清 NfL 的诊断截断值,单纯的升高并不能作为诊断标准。故目前血清 NfL 对于神经退行性疾病只能作为一个辅助诊

断标准, 间接用于监测疾病的进展。

本研究存在一定的局限性。第一, 部分 Meta 分析的异质性较大, 进一步的亚组分析未明确异质性来源, 除原始研究纳入量较少外, 也可能存在未知的影响因素。第二, 本研究仅对比了健康对照组与各类神经退行性疾病的血清 NfL 水平, 由于同时纳入多种神经退行性疾病的原始研究较少, 因此没有分析不同种类神经退行性疾病间的血清 NfL 水平。第三, 受原始研究的影响, 本研究仅对比了暴露组与非暴露组间的血清 NfL 水平, 无法得出血清 NfL 作为诊断标准时的截断值。

综上所述, 神经退行性疾病患者血清 NfL 水平较健康人群明显升高, 认知损害程度越大, 血清 NfL 水平越高, 血清 NfL 可能是神经退行性疾病潜在的外周生物标志物, 能够进一步反映认知水平的下降。

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