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RESEARCH ARTICLE

A β status assessment in a hypothetical scenario prior to treatment with disease-modifying therapies: Evidence from 10-year real-world experience at university memory clinics

Matthias Brendel^{1,2,3} | Tandis Parvizi^{1,4,5} | Johannes Gnörich¹ |
Christof Elias Topfstedt⁶ | Katharina Buerger^{2,6} | Daniel Janowitz⁶ |
Boris-Stephan Rauchmann⁷ | Robert Perneczky^{2,3,5,8,9} | Carolin Kurz⁷ |
Dirk Mehrens¹⁰ | Wolfgang G. Kunz¹⁰ | Julia Kusche-Palenga¹ |
Agnes Bernadette Kling¹ | Antonia Buchal¹⁰ | Elizabet Nestorova⁷ | Sara Silvaieh^{4,5} |
Raphael Wurm^{4,5} | Tatjana Traub-Weidinger^{11,12} | Sigrid Klotz^{5,13} |
Günther Regelsberger^{5,13} | Axel Rominger¹⁴ | Alexander Drzezga^{15,16,17} |
Johannes Levin^{2,3,18} | Elisabeth Stögmann^{4,5} | Nicolai Franzmeier^{3,6,19} |
Günter U. Höglinger^{2,3,18}

¹Department of Nuclear Medicine, LMU University Hospital, LMU Munich, Munich, Germany

²German Center for Neurodegenerative Diseases (DZNE) Munich, Munich, Germany

³Munich Cluster for Systems Neurology (SyNergy), Munich, Germany

⁴Department of Neurology, Medical University of Vienna, Vienna, Austria

⁵Comprehensive Center for Clinical Neurosciences and Mental Health, Medical University of Vienna, Vienna, Austria

⁶Institute for Stroke and Dementia Research (ISD), LMU University Hospital, LMU Munich, Munich, Germany

⁷Department of Psychiatry and Psychotherapy, LMU University Hospital, LMU Munich, Munich, Germany

⁸Ageing Epidemiology (AGE) Research Unit, School of Public Health, Imperial College London, London, UK

⁹Sheffield Institute for Translational Neuroscience (SITraN), University of Sheffield, Sheffield, UK

¹⁰Department of Radiology, LMU University Hospital, LMU Munich, Munich, Germany

¹¹Division of Nuclear Medicine, Department of Biomedical Imaging and Image-Guided Therapy, Medical University of Vienna, Vienna, Austria

¹²Department of Diagnostic and Therapeutic Nuclear Medicine, Klinik Donaustadt, Vienna, Austria

¹³Division of Neuropathology and Neurochemistry, Department of Neurology, Medical University of Vienna, Vienna, Austria

¹⁴Department of Nuclear Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

¹⁵Department of Nuclear Medicine, Faculty of Medicine and University Hospital Cologne, Cologne, Germany

¹⁶German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany

¹⁷Institute of Neuroscience and Medicine (INM-2), Molecular Organization of the Brain, Forschungszentrum Jülich, Jülich, Germany

¹⁸Department of Neurology, LMU University Hospital, LMU Munich, Munich, Germany

¹⁹The Sahlgrenska Academy, Institute of Neuroscience and Physiology, Department of Psychiatry and Neurochemistry, Mölndal and Gothenburg, University of Gothenburg, Mölndal, Sweden

Matthias Brendel, Tandis Parvizi, and Johannes Gnörich contributed equally as first authors.

Elisabeth Stögmann, Nicolai Franzmeier, and Günter U. Höglinger contributed equally as last authors.

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Correspondence

Matthias Brendel, Department of Nuclear Medicine, LMU University Hospital, LMU Munich, Marchioninistrasse 15, 81377 Munich, Germany.
Email:
matthias.brendel@med.uni-muenchen.de

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Abstract

INTRODUCTION: With the advent of disease-modifying therapies, accurate assessment of biomarkers indicating the presence of disease-associated amyloid beta ($A\beta$) pathology becomes crucial in patients with clinically suspected Alzheimer's disease (AD). We evaluated $A\beta$ levels in cerebrospinal fluid ($A\beta$ CSF) and $A\beta$ levels in positron emission tomography ($A\beta$ PET) biomarkers in a real-world memory-clinic setting to develop an efficient algorithm for clinical use.

METHODS: Patients were evaluated for AD-related $A\beta$ pathology from two independent cohorts (Ludwig Maximilian University [LMU], $n = 402$, and Medical University of Vienna [MUV], $n = 144$). Optimal thresholds of CSF biomarkers were deduced from receiver operating characteristic curves and validated against $A\beta$ PET positivity.

RESULTS: In both cohorts, a CSF $A\beta_{42/40}$ ratio $\geq 7.1\%$ was associated with a low risk of a positive $A\beta$ PET scan (negative predictive value: 94.3%). Implementing two cutoffs revealed 14% to 16% of patients with intermediate results (CSF $A\beta_{42/40}$ ratio: 5.5%–7.1%), which had a strong benefit from $A\beta$ PET imaging (44%–52% $A\beta$ PET positivity).

DISCUSSION: A two-cutoff approach for CSF $A\beta_{42/40}$ including $A\beta$ PET imaging at intermediate results provides an effective assessment of $A\beta$ pathology in real-world settings.

KEYWORDS

Alzheimer's disease, biomarkers, cerebrospinal fluid, dementia, positron emission tomography, real world

Highlights

- We evaluated cerebrospinal fluid (CSF) and positron emission tomography (PET) amyloid beta ($A\beta$) biomarkers for Alzheimer's disease in real-world cohorts.
- A CSF $A\beta_{42/40}$ ratio between 5.5% and 7.1% defines patients at borderline levels.
- Patients at borderline levels strongly benefit from additional $A\beta$ PET imaging.
- Two-cutoff CSF $A\beta_{42/40}$ and PET will allow effective treatment stratification.

1 | INTRODUCTION

With the possible approval of anti-amyloid therapies for Alzheimer's disease (AD) in Europe on the horizon, assessing the patient's extracellular amyloid beta ($A\beta$) status before initiating drug treatment is of utmost importance. According to currently approved tests, the $A\beta$ status can either be determined by $A\beta$ levels in cerebrospinal fluid (CSF) or by positron emission tomography (PET) with $A\beta$ radiotracers.¹ Costs, accessibility, and side effects of both assessments need to be considered together with the costs of $A\beta$ -lowering therapies to ensure proper access to current health-care systems. In this regard, it is also crucial to develop diagnostic algorithms that provide optimized accuracy at minimal cost. Several studies have compared diagnostic accuracies of CSF and PET assessments and found considerable agreement.^{2–5} However, regarding the determination of amyloid positivity, a discordance rate of 10% to 20% between these two modalities has been reported espe-

cially in earlier stages of the disease,^{6–9} thus creating uncertainty in clinical practice when only one investigation is performed at the individual patient level. The implementation of blood-based biomarkers may streamline the prognostic and diagnostic work-up of AD and further reduce the number of invasive or cost-intensive examinations in the future.

Real-world scenarios that allow conclusions of $A\beta$ status assessment at the individual patient level on an on-demand basis are still rare. Thus, we aimed to investigate 10-year real-world data of memory clinics at tertiary centers comprising two independent German and Austrian cohorts with the goal to set up an efficient algorithm for $A\beta$ status assessment. We used CSF $A\beta$ and $A\beta$ PET as currently approved tests as a timely scenario due to the imminent approval of anti-amyloid antibodies in Europe, but we note that integration of blood-based biomarkers into the proposed two-cutoff approach will be straightforward upon approval.

2 | METHODS

2.1 | Study design and patient cohort

This retrospective, cross-sectional, bicentric study included participants from two independent cohorts: patients recruited through three specialized outpatient clinics at the Ludwig Maximilian University (LMU) hospital (Department of Psychiatry and Psychotherapy, Department of Neurology, Institute of Stroke and Dementia Research), $n = 402$, and the memory clinic of the Department of Neurology, Medical University of Vienna (MUV), $n = 144$. The German cohort included cognitively unimpaired individuals (either no objective cognitive concerns or subjective cognitive decline [SCD]) and cognitively impaired patients (categorized as having mild cognitive impairment [MCI], probable AD dementia, or other neurodegenerative disorders). Diagnoses of MCI and probable AD dementia were based on core clinical criteria according to the recommendations of the National Institute on Aging and Alzheimer's Association (NIA-AA).^{10,11} Patients with subjective cognitive complaints who did not fulfill criteria for MCI were classified as SCD. Patients with non-AD neurodegenerative disorders fulfilled clinical criteria for frontotemporal dementia,¹² non-fluent or semantic primary progressive aphasia,¹³ corticobasal syndromes,¹⁴ progressive supranuclear palsy,¹⁵ and vascular dementia.¹⁶ The Austrian cohort consisted of cognitively impaired patients with a clinical diagnosis of MCI due to AD and probable AD dementia, based on core clinical criteria according to the NIA-AA recommendations.^{10,11}

In the German cohort, subgroup analyses were performed in all patients with cognitive impairment (AD and non-AD neurodegenerative disorders, $n = 351$) and patients with a clinical diagnosis along the AD continuum (i.e., MCI due to AD and probable AD dementia, $n = 303$). In a next step, we combined patients with MCI and mild dementia (Mini-Mental State Examination [MMSE] > 20 , functional impact mainly on instrumental activities of daily life),¹⁷ as this group of patients with early symptomatic cognitive decline would be potential candidates for anti-amyloid therapies.

In addition to a thorough standardized diagnostic examination including neurological evaluation, neuropsychological testing, magnetic resonance imaging (MRI), and basic laboratory testing, all patients underwent A β PET imaging and CSF analyses of established AD biomarkers (A β 42, A β 40, total tau [t-tau], and phosphorylated tau 181 [p-tau181]). On this basis, the amyloid ratio (A β 42/40) was determined.

2.2 | Neuropsychological examination

Assessment of cognitive function and analysis of different domains were conducted using the Neuropsychological Test Battery Vienna (NTBV) and the Vienna Visuo-Constructional Test 3.0 (VVT 3.0)^{18–20} at the Department of Neurology, MUV. Adequate normative data from cognitively unimpaired individuals were available, and z scores for each variable were calculated and corrected for age, education, and sex. Depressive symptoms were assessed using the Beck Depres-

RESEARCH IN CONTEXT

- 1. Systematic Review:** The authors systematically reviewed the literature using PubMed. In light of the imminent approval of disease-modifying therapies in Europe, accurate and timely identification of patients who would benefit from these treatments is of great importance. Although growing evidence shows consistent results between currently approved biomarkers in cerebrospinal fluid (CSF) and positron emission tomography (PET) imaging in up to 90%, the widespread use of these biomarkers is still limited, and algorithms on an individual patient level are scarce.
- 2. Interpretation:** We show that the implementation of a two-cutoff approach would substantially reduce the amount of additional biomarker testing. In both cohorts, a CSF amyloid beta (A β)42/40 ratio $\geq 7.1\%$ was associated with a low risk of A β PET positivity, thus excluding an underlying amyloid pathology with a high negative predictive value. Patients exhibiting intermediate CSF A β 42/40 results would benefit from additional PET imaging.
- 3. Future Directions:** Follow-up studies regarding patients with intermediate and discordant results will be necessary, for example, with quantification tools for PET imaging or ultrasensitive immunoassays in CSF and blood, to better determine the diagnostic and prognostic value of these findings in a real-world setting before administration of anti-amyloid therapies.

sion Inventory (BDI-II).²¹ Similar assessments were performed at the Department of Psychiatry and Psychotherapy, LMU.

At the Institute for Stroke and Dementia Research, LMU, and the Department of Neurology, LMU, cognitive assessments were conducted using the Consortium to Establish a Registry for Alzheimer's Disease (CERAD-NP) Plus battery, consisting of a standardized set of neuropsychological tests including MMSE, word list learning test, Trail Making Test Parts A and B, and word fluency test.^{22,23}

The clinical distinction between MCI and dementia was determined by the results of neuropsychological testing, as well as the assessment of the individual's ability to perform activities of daily living.

2.3 | CSF AD biomarkers

CSF was obtained by lumbar puncture and handled based on current international recommendations.²⁴ Concentrations of A β 42, A β 40, p-tau181, and t-tau in CSF were measured using commercially available enzyme-linked immunosorbent assays (ELISA; Innostest beta-amyloid 1-42, Innostest beta-amyloid 1-40, Innostest phosphoTAU 181p, and Innostest hTAU Ag, Fujirebio Europe).^{25,26}

2.4 | A β PET imaging

A β PET imaging was performed at the Department of Nuclear Medicine, LMU, and the Division of Nuclear Medicine, MUV. [18 F]flutemetamol A β PET scans (LMU and MUV; average dose: 182 ± 11 MBq), [18 F]florbetaben A β PET (LMU; average dose: 288 ± 14 MBq) or [11 C]Pittsburgh compound-B (PiB, MUV; average dose 400 MBq) were performed 90 to 110 minutes ([18 F]flutemetamol and [18 F]florbetaben) or 40 to 60 minutes (PiB) after injection on a Siemens Biograph 64 PET. Low-dose computed tomography (CT) was acquired for attenuation correction. Scans were evaluated daily by a visual read (resident with validation by an attending as an expert reader with > 500 evaluated A β PET scans) as positive or negative for the presence of cortical A β pathology. In the majority of the cases, attendings evaluated the scan blinded to the resident's opinion. Both resident and attending physicians received certified reader training for the interpretation of [18 F]flutemetamol (Vizamyl) and [18 F]florbetaben (Neuraceq) scans, following the guidelines and recommendations provided in the summary of product characteristics. PET images of [18 F]flutemetamol and PiB were analyzed using a rainbow color scale, while [18 F]florbetaben images were analyzed using a grayscale. The readers manually adjusted the threshold window using the pontine/cerebellar white/gray matter contrast as a reference. All readers had access to clinical information and morphology (i.e., MRI in $\approx 80\%$, CT in $\approx 20\%$). All images were systematically evaluated, starting at the level of the pons/cerebellum and moving upward through the frontal lobes, anterior cingulate, posterior cingulate, precuneus, temporoparietal regions (including the insula and lateral temporal lobes), including the striatal region for [18 F]flutemetamol and PiB scans. The interpretation was performed visually by comparing the tracer uptake in cortical gray matter to that in adjacent cortical white matter. If any of these regions showed clear positive (abnormal) activity, the image was classified as positive; otherwise, it was classified as negative. Semiquantitative A β PET data were additionally available for [18 F]flutemetamol and [18 F]florbetaben as supporting information to the readers, expressed as z scores in A β PET target regions (frontal, parietal, temporal, posterior cingulate cortex) and their composite. The pons was used as reference tissue for [18 F]flutemetamol and the cerebellar cortex was used as reference tissue for [18 F]florbetaben. In discrepant cases, the visual interpretation of the attending was decisive (< 15%). The attending regularly consulted a second attending before final decision making in discrepant cases.

2.5 | Statistical analysis

Diagnostic accuracy of CSF biomarkers for predicting the dichotomous A β PET result were assessed using receiver operating characteristic (ROC) curves. In this study, A β PET positivity determined by visual read was considered the standard of truth for A β status because agreement of A β PET with autopsy validation was 95% to 96% in phase 3 studies.^{27,28} The predefined thresholds were successfully validated with A β PET positivity as the standard of truth for the investigated

cohorts. Determination of optimal cutoffs was deduced from ROC analyses. A *P* value of < 0.05 was interpreted as statistically significant. All calculations were performed in SPSS (version 29.0.1.0, IBM).

3 | RESULTS

3.1 | Classification of A β PET status and predictive value of CSF biomarkers in the German cohort

Detailed characteristics of both cohorts are summarized in Table 1.

Considered alone, CSF A β 42 levels (changing cutoff during the 10-year period: 375/450 pg/mL) demonstrated very low sensitivity (14.6%) and high specificity (94.7%) in detecting positivity in A β PET at the individual patient level in the German cohort. The CSF A β 42/40 ratio (cutoff: 5.5%) showed superior performance, with 86.7% sensitivity and 87% specificity. CSF p-tau181 (cutoff: 61 pg/mL) showed a sensitivity of 74.1% in detecting positivity in A β PET, with a specificity of 67.1%. Additionally, the optimal cutoff values for the CSF biomarkers in this cohort were determined. These were calculated as 5.5% for the CSF A β 42/40 ratio (area under the curve [AUC] = 0.92, 95% confidence interval [CI] = 0.89–0.95, *P* < 0.001), 689 pg/mL for CSF A β 42 (AUC = 0.85, 95% CI = 0.81–0.89, *P* < 0.001), and 63.4 pg/mL for CSF p-tau181 (AUC = 0.78, 95% CI = 0.74–0.83, *P* < 0.001).

Next, we focused on patients with discrepant classification between A β PET and CSF to determine an optimized algorithm for the determination of the individual A β status. Considering the A β 42/40 ratio the CSF test with the best performance (negative predictive value [NPV] 82.6%, positive predictive value [PPV] 90.2%), 31 of 178 (17.4%) patients did not show evidence of AD-related A β pathology in the CSF A β 42/40 ratio based on a 5.5% threshold but a positive A β PET scan. Furthermore, 22 of 224 patients (9.8%) with diagnostic CSF A β 42/40 ratio (i.e., a ratio $\leq 5.5\%$) exhibited a negative A β PET scan.

Within the subgroup of CSF A β 42/40 ratio non-diagnostic cases (CSF A β 42/40 ratio > 5.5%), a data-driven cutoff of 7.1% discriminated best between A β PET positive and negative cases (*n* = 178, AUC = 0.85, 95% CI = 0.77–0.93, *P* < 0.001, Figure 1). Patients with a CSF A β 42/40 ratio between 5.5% and 7.1% (*n* = 55, 13.7%) revealed A β PET positivity in 43.6%, meaning that only 2.3 patients of this subpopulation had to be scanned to identify an additional case with A β positivity. To the contrary, patients with a CSF A β 42/40 ratio $\geq 7.1\%$ (*n* = 123, 30.6%) showed only 5.7% cases with A β PET positivity, indicating that 17.5 patients of this subpopulation would need to be scanned to detect an additional case with A β positivity (Figure 1). Subgroup analyses in patients with all-cause cognitive impairment (*n* = 351) and a clinical diagnosis of AD (MCI due to AD and probable AD dementia, *n* = 303) confirmed the value of a two-cutoff approach (Figures S1 and S2 in supporting information).

In contrast, within the subgroup of CSF A β 42/40 ratio-positive patients (*n* = 224), no suitable cutoff value was identified to detect discrepant cases (9.8%) with negative A β PET (AUC = 0.61, 95% CI = 0.47–0.76, *P* = 0.129; Figure 1). The application of two cutoffs resulted in a higher NPV (94.3%), while the PPV remained unchanged (90.2%).

TABLE 1 Patient characteristics of the German and Austrian cohort.

| | German cohort <i>n</i> = 402 | Austrian cohort <i>n</i> = 144 |
|---|---------------------------------|-----------------------------------|
| Age | 70.9 (64.2–76.1) | 66.4 (59.3–75.1) |
| Sex (f) | 189 (47%) | 70 (48.6%) |
| MMSE | 26 (23–28) | 26 (22–28) |
| Amyloid PET tracer | | |
| [¹⁸ F]florbetaben | 86 (21.4%) | – |
| [¹⁸ F]flutemetamol | 316 (78.6%) | 67 (45.6%) |
| [¹¹ C]Pittsburgh compound B | – | 77 (53.5%) |
| Diagnoses | | |
| CU/SCD | 51 (12.7%) | – |
| MCI/AD dementia (mild) | 267 (66.4%) | 124 (86.1%) |
| AD dementia (moderate-severe) | 36 (9.0%) | 20 (13.9%) |
| Non-AD neurodegenerative disorders* | 48 (11.9%) | – |

Note: Data are presented as median and interquartile range (25th to 75th percentile) or *n* (%).

Abbreviations: AD, Alzheimer's disease; CU, cognitively unimpaired; f, female; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; PET, positron emission tomography; SCD, subjective cognitive decline.

*Non-AD neurodegenerative disorders included patients with frontotemporal dementia, primary progressive aphasia, corticobasal syndrome, progressive supranuclear palsy and vascular dementia. Patients were categorized either as MCI /mild dementia (*n* = 41) or moderate to severe dementia (*n* = 7).

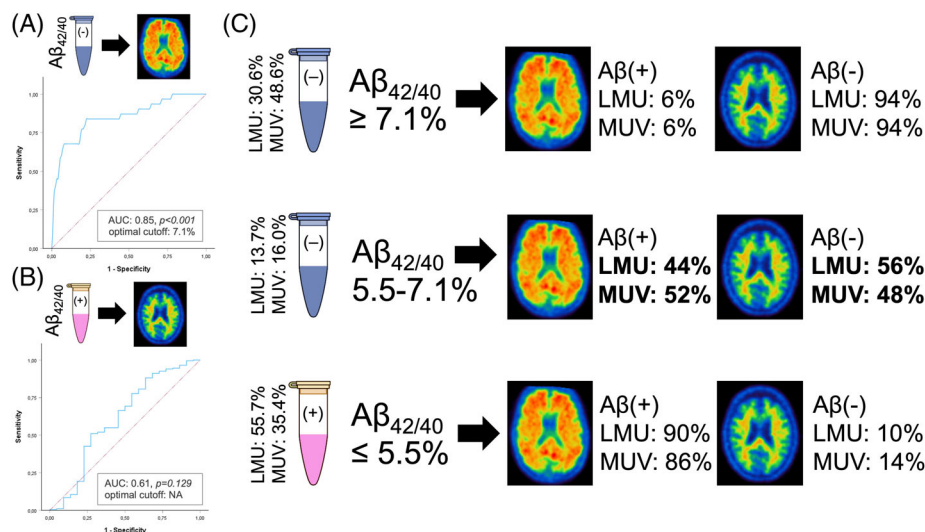


FIGURE 1 Data-driven cutoff for the CSF A β _{42/40} ratio regarding A β PET positivity and evaluation of a two-cutoff approach in the German (LMU) and Austrian (MUV) cohort. ROC curves were constructed to determine the optimal cutoff for the CSF A β _{42/40} ratio in predicting A β PET positivity in the CSF A β _{42/40} negative cohort (> 5.5%, A) and positive cohort (\leq 5.5%, B). These data-driven thresholds were further used to implement two cutoffs, which categorized patients as at low, intermediate, and high risk of harboring a positive A β PET scan (C). AUC, area under the curve; A β , amyloid beta; CSF, cerebrospinal fluid; LMU, Ludwig Maximilian University; MUV, Medical University of Vienna; PET, positron emission tomography; ROC, receiver operating characteristic

3.2 | Performance of CSF biomarkers regarding cerebral A β PET status in the Austrian validation cohort

In the Austrian cohort, both CSF A β ₄₂ (cutoff 500 pg/mL) and CSF A β _{42/40} (cutoff 7.0%) demonstrated higher sensitivity (80% and

93.3%, respectively) but lower specificity (65.5% and 79.8%, respectively) in detecting cerebral amyloidosis on A β PET imaging compared to the German cohort. CSF p-tau181 (cutoff 61 pg/mL) showed a sensitivity of 81.7% and specificity of 85.7% to detect positivity in A β PET.

Similar to the German cohort, CSF A β _{42/40} showed the best performance (NPV 94.4%, PPV 76.7%) regarding the prediction of

positivity in A β PET imaging. By applying the predefined threshold of 7.0%, 21 out of 144 patients (28.9%) yielded discordant results (A β 42/40 > 7.0% and positive A β PET scan 5.6%, A β 42/40 \leq 7.0% and negative A β PET scan 23.3%). Using the predefined threshold of the German cohort (cutoff \leq 5.5%), 23 of 144 patients (30.9%) yielded discordant results (A β 42/40 > 5.5% and positive A β PET scan 17.2%, A β 42/40 \leq 5.5% and negative A β PET scan 13.7%), resulting in an NPV of 82.8% and PPV of 86.3%.

When the optimized two-cutoff approach of the German cohort was applied (\leq 5.5% and \geq 7.1%), 16% of the patients were classified in the intermediate range, again with a high frequency of a positive A β PET scan in 52.2% of these cases. Notably, in patients with a CSF A β 42/40 ratio \geq 7.1%, only 5.7% of the patients showed positive A β PET scans, which is consistent with the findings of the German cohort. Comparing the two-cutoff approach with the threshold of the Austrian cohort (7.0%), the NPV remained high (94.3%), while the PPV was improved (86.3%).

3.3 | Diagnostic accuracy of CSF A β 42/40 in predicting A β PET status in early symptomatic cognitive decline

In the next step, we focused on patients with MCI and mild dementia in the German cohort ($n = 308$). By applying a threshold of 5.5% for the CSF A β 42/40 ratio, 28 of 122 patients (23%) showed discordant results, with positive A β PET scans and a ratio > 5.5%. Furthermore, 18 of 186 patients (9.7%) exhibited a ratio \leq 5.5% with no evidence of cerebral amyloidosis in A β PET imaging.

In this cohort, the optimal cutoff value for the CSF A β 42/40 ratio was 5.4% (AUC = 0.90, 95% CI = 0.86–0.94, $P < 0.001$), resulting in a sensitivity of 84.7%, specificity of 85.7%, NPV of 76.2%, and PPV of 91.2%. Additionally, in the subgroup of patients with a negative CSF ratio (i.e., > 5.5%, $n = 122$), a cutoff value of 7.2% differentiated best between A β PET positive and negative cases (AUC = 0.85, 95% CI = 0.76–0.94, $P < 0.001$).

Using both data-driven cutoffs, 15.6% of the patients ($n = 48$) obtained intermediate results (ratio between 5.4% and 7.2%), indicating positive A β PET scans in 52.1%. Notably, in those with a ratio \geq 7.2%, positive A β PET scans were revealed only in 6.4%. Again, the two-cutoff approach acquired a higher NPV (93.6%), while the PPV remained unchanged (91.2%).

In the subgroup of early symptomatic patients with MCI due to AD and mild AD dementia ($n = 267$), who would be in-label candidates for anti-amyloid therapies, the optimal cutoff for the CSF A β 42/40 ratio was 5.3% (AUC = 0.89, 95% CI = 0.83–0.94, $P < 0.001$). In patients with a negative CSF ratio (i.e., > 5.5%, $n = 84$) a data-driven cutoff of 7.1% distinguished best between A β PET positive and negative cases (AUC = 0.89, 95% CI = 0.81–0.97, $P < 0.001$). Using both calculated thresholds, 16.1% of patients showed a CSF ratio in the intermediate range (i.e., CSF A β 42/40 between 5.3% and 7.1%) with A β PET positivity in 62.8% of cases (Figure S3 in supporting information). Above a ratio of 7.1%, 10% of patients

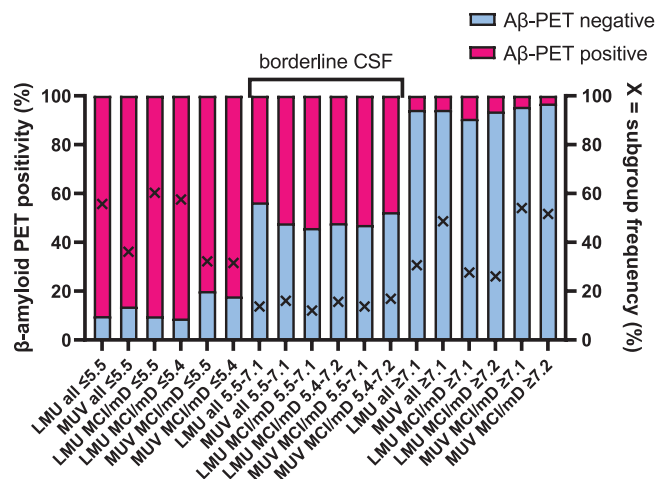


FIGURE 2 Discrepancies of cerebral A β status based on PET and CSF results in both cohorts at different cutoffs as well as proportions of A β PET positive and negative findings in the proposed borderline range of CSF A β 42/40. Findings are displayed in both whole cohorts and subsets of early symptomatic patients. Frequencies of each group are illustrated in each bar (marked with X). A β , amyloid beta; CSF, cerebrospinal fluid; LMU, Ludwig Maximilian University; MCI, mild cognitive impairment; mD, mild dementia; MUV, Medical University of Vienna; PET, positron emission tomography

exhibited positive A β PET scans, resulting in an NPV of 90% and PPV of 93.1%.

In MCI and mild dementia cases of the Austrian cohort ($n = 124$), a CSF A β 42/40 threshold of 7.0% resulted in a sensitivity of 93.2%, specificity of 81.3%, NPV of 95.6%, and PPV of 73.2%. Discordant results were obtained in 18 patients (31.2%; A β 42/40 > 7.0% and positive A β PET scan: 4.4%, A β 42/40 \leq 7.0% and negative A β PET scan: 26.8%). The predefined threshold of 5.4% of the German cohort led to an improvement of the PPV (82.1%), but a deterioration of the NPV (85.9%). The proportion of patients with discordant results remained similar ($n = 19$, 32%), with more patients exhibiting positive A β PET scans and a ratio > 5.4% (14.1%) and fewer patients with a ratio \leq 5.4% and negative A β PET scans (17.9%). When applying both predefined cutoffs (\leq 5.4% and \geq 7.2%), 21 out of 124 patients (16.9%) ranged between the two cutoffs, with positive A β PET scans in 47.6%. Above the ratio of 7.2%, only 3.1% showed positive A β PET scans. Compared to the threshold of the Austrian cohort (7.0%), both NPV (96.9%) and PPV (82.1%) were improved. Figure 2 summarizes discrepancies between A β status definition by PET and CSF in both cohorts at different cutoffs as well as proportions of A β PET positive and negative findings in the proposed borderline range of CSF A β 42/40.

4 | DISCUSSION

In this retrospective study, we aimed to evaluate the diagnostic workflow for the assessment of cerebral A β status in a real-world memory-clinic setting in two independent cohorts. Using A β PET as the standard of truth, we identified borderline cases with a high

probability of A β PET positivity despite non-diagnostic CSF. By applying a two-cutoff approach based on the CSF A β 42/40 ratio, we categorized patients as exhibiting a low, intermediate, and high probability of having an abnormal A β PET scan that could guide diagnostic algorithms of A β status determination in memory clinics.

Recent studies have also proposed the application of a two-cutoff threshold to improve the diagnostic accuracy of fluid biomarkers.^{29–31} This would enhance the diagnostic certainty as well as reduce the number of additional confirmatory biomarker testing. The main finding of our study was that in both cohorts, patients with a CSF A β 42/40 ratio $\geq 7.1\%$ had a low risk of harboring a positive A β PET scan, resulting in a high NPV of 94.3%. In line with current proposed European recommendations regarding biomarker-based diagnosis,¹ these results would exclude an underlying AD pathology and require a reconsideration of the diagnostic suspicion.

In both cohorts, a small but relevant proportion of patients (13.7% and 16.0%) showed intermediate results (i.e., CSF A β 42/40 ratio between 5.5%–7.1%), thus representing a group that should undergo additional A β PET imaging after CSF assessment to reevaluate brain amyloidosis and identify those patients who would benefit from anti-amyloid therapies. Future studies may also determine which patients should be referred to A β PET directly and which should receive CSF assessment first. Notably, these borderline cases may display patients with intermediate values not just in CSF but across different diagnostic modalities, particularly A β PET imaging, which could indicate the presence of an early AD-related neuropathological change in these patients.²⁹ Quantification of A β PET imaging and further standardization of collected data to reduce variability across tracers and sites (i.e., Centiloid Project)³² may be of benefit in the future.

A CSF A β 42/40 ratio $\leq 5.5\%$ was considered A β positive in both study populations, with just a small proportion of patients exhibiting discordant A β PET results (i.e., negative, 9.8% and 13.7%). This may be in line with the hypothesis that a change of CSF A β 42 and CSF A β 42/40 occurs before the accumulation of dense, fibrillar A β plaques visualized by A β PET imaging, as both tests are likely assessing different species and states of A β accumulation.³³ In clinical practice, the concomitant assessment of CSF p-tau181 could potentially aid in ascertaining the detected brain amyloidosis as the underlying cause of the cognitive impairment, as tau pathology is the second essential proteinopathy required for the neuropathological diagnosis of AD.^{1,17} Furthermore, the A β 42/p-tau181 ratio has also demonstrated high concordance with A β PET imaging and is therefore included in the clinical routine assessments of CSF biomarkers in many memory clinics, particularly when A β 40 is not available.^{2,34–36}

In line with the whole study cohort, the values of the optimized thresholds remained unchanged in the subgroup of patients with cognitive impairment (CSF A β 42/40 ratio $\leq 5.5\%$ and $\geq 7.1\%$). The number of patients with intermediate CSF A β 42/40 results was similar (13.4%), displaying positive A β PET scans in half of these cases, further emphasizing the need for additional biomarker testing in this patient group. In patients with a clinical AD diagnosis, the lower threshold for the CSF A β 42/40 ratio was calculated as 5.3%, while the upper threshold remained the same ($\geq 7.1\%$); 16.5% of patients showed intermediate

CSF results with an even higher rate of positive A β PET scans in this group. Patients with a CSF A β 42/40 ratio $\geq 7.1\%$ showed positive A β PET results in 9.3% of patients, resulting in a slightly lower NPV of 90.7%, while the PPV was higher than in the whole cohort (93.5%). Similar results were obtained in the group of patients with MCI and mild dementia due to AD. This could be explained by the fact that the prevalence of amyloid positivity was higher in the group of patients with clinically suspected AD compared to the other groups that were analyzed. This led to a distinctly smaller group of amyloid-negative patients, which could potentially influence these results. However, it exemplifies the real-world setting of memory clinics, in which amyloid testing in CSF and PET imaging is not routinely performed in all patients with cognitive impairment.

When focusing on patients with early symptomatic all-cause dementia (i.e., MCI and mild dementia), the data-driven optimal cutoffs of the CSF A β 42/40 ratio only slightly shifted to 5.4% and 7.2%, which may indicate the need for different thresholds depending on the clinical stage of the disease. The rate of intermediate results remained similar (15.6% and 16.9%), with only a few patients exhibiting a positive A β PET scan above the threshold of 7.2% (6.4% and 3.1%, NPV 93.6% and 96.9%).

In terms of predicting A β PET positivity, the CSF A β 42/40 ratio demonstrated higher performance than the individual CSF biomarkers alone, which is consistent with previously published studies and might be explained by the control of interindividual variations regarding the natural fluctuations of the proteins as well as preanalytical factors.^{2,35,37}

The recent US Food and Drug Administration approval of disease-modifying therapies in the United States has emphasized the urgent need for an accurate and timely diagnosis of AD pathology in patients with cognitive impairment. The use of currently available biomarkers is still limited due to the high costs of PET imaging and the invasiveness of CSF analysis, which hampers their widespread routine application. Additionally, a biomarker-based approach is reliant on geographic differences, particularly in terms of availability, accessibility, and feasibility.^{38–40} Consequently, the decision on which biomarkers to use is frequently guided more by organizational and logistical considerations than by clinical and patient-related factors.^{1,41,42} Furthermore, the application of multiple biomarkers may complicate the diagnostic process, making it challenging for clinicians to interpret the results. Thus, it is of great importance to implement an algorithm for routine clinical practice.

Although many studies show a strong concordance between CSF A β biomarkers and A β PET status, clinicians often encounter discordant results between these two investigations in everyday practice, which causes difficulties in the clinical routine for the specific diagnosis of individual patients. This issue will become even more relevant in the future when targeted therapies depend on it. Blood-based biomarkers may be of great value in the future regarding screening and risk stratification of patients with cognitive impairment but they still need to undergo validation in real-world cohorts before clinical implementation. Hence, appropriate use of available resources is crucial to ensure an accurate diagnosis with the lowest number of examinations.

The proposed workflow with a two-cutoff approach could assist in both confirming (rule in) as well as excluding (rule out) the presence of AD-related amyloid pathology and further identify those patients who would need additional biomarker testing before administration of anti-amyloid therapies. Future steps will need to improve methodologies and harmonize quantitative analyses of fluid biomarkers to establish standardized cutoffs and reference values across different assays and laboratories to grant equivalent and reliable results.⁴³ Because A β PET imaging in clinical practice is visually assessed for the absence or presence of A β deposits, interrater variability can display a problem, especially in borderline cases.⁴⁴ The implementation of new tracers and additional quantification tools could aid in providing a standardized quantitative measure for amyloid burden, allowing a better comparison across different tracers and sites, and facilitating fast and consistent analysis. In addition, A β PET imaging may gain a new significance once anti-amyloid therapies are approved in Europe, as the duration of the administration may depend on the removal of cerebral amyloid plaques visualized and quantified by PET imaging, which could lead to fewer infusions and lower treatment costs.^{45–47}

The main strength of our study is the replication of our real-world data in an independent real-world cohort, which supports the generalizability of the proposed two-cutoff approach. This approach is ready to use in imminent anti-amyloid therapy evaluation. However, several limitations must be acknowledged. As classification of A β PET scan was assessed through visual read, we did not include quantification data, which would be of special interest in discordant and intermediate results. Furthermore, we did not obtain longitudinal analyses of CSF biomarker concentrations or plasma biomarkers. During the conduct of our study, analyses of core AD biomarkers in CSF were performed with commercially available ELISA in both cohorts. Hence, it would be of great interest to further validate the obtained results on automated platforms.

Due to the cross-sectional design of the study, we lack follow-up data on clinical outcomes to assess future cognitive decline and disease progression in cognitively unimpaired individuals. Our results do not clarify if specific patient subpopulations should undergo A β PET imaging before CSF assessment.

5 | CONCLUSION

In conclusion, our data demonstrate the utility of a two-cutoff approach for CSF A β 42/40 assessment in a real-world setting of two independent cohorts. This approach would enhance the detection and, more importantly, exclusion of underlying amyloid pathology, especially in patients with MCI or mild dementia. Furthermore, we identified patients with borderline CSF results (14%–16%), who would strongly benefit from additional A β PET biomarker testing, and ultimately, reduce the number and costs of further examinations.

AUTHOR CONTRIBUTIONS

Matthias Brendel: conceptualization, validation, writing—original draft, visualization, supervision, project administration, funding

acquisition; Tandis Parvizi and Johannes Gnörich: methodology, software, formal analysis, writing—original draft, visualization; Christof Elias Topfstedt: investigation, formal analysis; Katharina Buerger: investigation, resources; Daniel Janowitz: investigation, resources; Boris-Stephan Rauchman: investigation, resources; Robert Perneczky: investigation, resources, writing—review & editing, supervision; Carolin Kurz: investigation, resources; Dirk Mehrens: conceptualization, Wolfgang G. Kunz: conceptualization; Julia Kusche-Palenga: methodology, data curation; Agnes Bernadette Kling: methodology, data curation; Antonia Buchal: methodology, software, data curation; Elizabet Nestorova: methodology, software, data curation; Sara Silvaieh: resources; Raphael Wurm: resources; Tatjana Traub-Weidinger: resources; Sigrid Klotz: resources; Günther Regelsberger: resources; Axel Rominger: conceptualization, resources, funding acquisition; Alexander Drzezga: conceptualization, writing—review & editing, project administration; Johannes Levin: conceptualization, writing—review & editing, project administration; Elisabeth Stögmann: conceptualization, writing—review & editing, supervision, project administration; Nicolai Franzmeier: conceptualization, formal analysis, writing—review & editing, supervision, project administration; Günter U. Höglinger: conceptualization, writing—review & editing, supervision, project administration, funding acquisition.

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CONFLICT OF INTEREST STATEMENT

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(all to the institution); consulting fees from Biogen, Eisai, and Lilly; support for attending meetings and/or travel from Roche; and has received payment for lectures, presentations, speakers bureaus, manuscript writing, or educational events by Biogen, Roche, Eisai, and Novartis. E.S. has participated on advisory boards (Biogen, Roche, Eisai, Sanofi) and held leadership or a fiduciary role in scientific societies (Austrian Alzheimer Association, the EAN scientific panel dementia). J.L. reports speaker fees from Bayer Vital, Biogen, EISAI, TEVA, Esteve, Zambon, and Roche; consulting fees from Axon Neuroscience, EISAI, and Biogen; author fees from Thieme medical publishers and W. Kohlhammer GmbH medical publishers; and is an inventor in a patent "Oral Phenylbutyrate for Treatment of Human 4-Repeat Tauopathies" (EP 23 156 122.6) filed by LMU Munich. In addition, he reports compensation for serving as chief medical officer for MODAG GmbH, is a beneficiary of the phantom share program of MODAG GmbH, and is an inventor in a patent "Pharmaceutical Composition and Methods of Use" (EP 22 159 408.8) filed by MODAG GmbH, all activities outside the submitted work. M.B. is a member of the Neuroimaging Committee of the EANM. M.B. received speaker honoraria from Roche, GE Healthcare, and Life Molecular Imaging and served as an advisor of MIAC and Life Molecular Imaging. N.F. has received speaker honoraria from Eisai, GE Healthcare, Life Molecular Imaging, and Consulting Honoraria from MSD. R.P. has received honoraria for advisory boards and speaker engagements from Roche, EISAI, Eli Lilly, Biogen, Janssen-Cilag, Astra Zeneca, Schwabe, Grifols, Novo Nordisk, and Tabuk. W.G.K. reports consulting fees from BMS, Boehringer Ingelheim, Need Inc., mintMedical, and FalkFoundation (unrelated to the paper). All other authors declare no competing interests. Author disclosures are available in the [supporting information](#).

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The study was approved by the Ethics Committee of the LMU Hospital (399-09 and 17-569) and the Medical University of Vienna (EK 1965/2019) and conducted in accordance with the Declaration of Helsinki.

CONSENT STATEMENT

Written informed consent was obtained from all patients.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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