Clinical utility of cerebrospinal fluid biomarkers in the evaluation of cognitive impairment: a systematic review and meta-analysis

Jemma Hazan, Michelle Wing, Kathy Y Liu, Suzanne Reeves, Robert Howard

ABSTRACT

Background The analytical and clinical validity of cerebrospinal (CSF) biomarkers has been extensively researched in dementia. Further work is needed to assess the ability of these biomarkers to improve diagnosis, management and health outcomes in the clinical setting.

Objectives To assess the added value and clinical utility of CSF biomarkers in the diagnostic assessment of cognitively impaired patients under evaluation for Alzheimer’s disease (AD).

Methods Systematic literature searches of Medline, EMBASE, PsycINFO and Web of Science research databases were conducted on 17 December 2022. Data from relevant studies were extracted and independently screened for quality using a tool for bias. Clinical utility was measured by clinicians’ changes in diagnosis, diagnostic confidence and patient management (when available), after their examination of patients’ CSF biomarkers. Cost-effectiveness was assessed by consideration of additional cost per patient and quality-adjusted life years.

Results Searches identified 17 studies comprising 2090 patient participants and 593 clinicians. The meta-analysis revealed that clinicians’ use of CSF biomarkers resulted in a pooled percentage change in diagnosis of 25% (95% CI 14 to 37), an increase in diagnostic confidence of 14% (95% CI 9 to 18) and a pooled proportion of patients whose management changed of 31% (95% CI 12 to 50). CSF biomarkers were deemed cost-effective, particularly in memory services, where pre-test AD prevalence is higher compared with a primary care setting.

Conclusions CSF biomarkers can be a helpful additional diagnostic tool for clinicians assessing patients with cognitive impairment. In particular, CSF biomarkers consistently improved clinicians’ confidence in diagnosing AD and influenced on diagnostic change and patient management. Further research is needed to study the clinical utility of blood-based biomarkers in the clinical setting.

INTRODUCTION

There are over 850 000 people with dementia in the UK,1 and numbers are expected to rise as the population ages, with over 1.1 million people living with AD in the UK by 2025. The diagnosis of Alzheimer’s disease (AD), which is the most common form of dementia, has advanced in the last decade through the availability of in vivo biological measures or ‘biomarkers’. These biomarkers can detect the pathological hallmarks of AD: pathological tau and beta amyloid proteins, as well as neurodegeneration.2 Biomarkers have been incorporated into the diagnostic framework of AD in clinical research.3 A consensus ‘roadmap’ was set out in 2017 to aid the incorporation of these biomarkers into the clinical setting to improve diagnostic accuracy.4

Cerebrospinal fluid (CSF) biomarkers are currently used in the diagnostic investigation of AD at specialist tertiary Neurology Centres in the UK.5 However, they are not routinely used in UK Memory Services.6 7 CSF biomarkers have demonstrated analytical validity.8 9 Validated AD CSF biomarkers include amyloid-β1–42, total-tau and phosphorylated-tau181 (ptau-181).10 A reduction in Aβ42 and raised levels of ptau are indicative of Aβ and tauopathologies in AD, while increased total-tau is a non-specific marker of neuronal injury.11 Many studies have demonstrated the correlation between CSF levels and neuropathology.12 13 14 15 These CSF biomarkers have garnered attention as, in contrast to imaging biomarkers such as amyloid PET, they are cheap, quick and simple to obtain in a clinical setting.16 However, there are reported concerns regarding lumbar puncture (LP) due to its perceived more invasive nature. The most frequent reported side effect is a post-LP headache.17 Several large multicentre studies have demonstrated that LP is a safe and tolerable procedure.17 18 Further barriers to the routine use of LP in Memory Services include a lack of skills training in this procedure.19

Biomarkers may also assist clinicians in differentiating AD from non-AD dementias, and mild cognitive impairment (MCI) from early AD.20 21 22 There have been several studies exploring the validity and diagnostic accuracy of CSF biomarkers in AD.23 However, to date, this may be one of the first systematic reviews to explore the clinical utility of CSF biomarkers in the diagnostic evaluation of cognitively impaired patients. In this study, we aim to assess the real-world added value and clinical utility, defined as relative improvement in clinicians’ diagnostic confidence or change in diagnosis or...
Two authors (JH and MW) independently extracted data. If there was a disagreement, this was resolved in discussion between the two raters. We extracted data on study characteristics (design, setting, duration, intervention, inclusion criteria), relevant outcomes (change in diagnosis, diagnostic confidence and change in management plan) and participant characteristics (population, sample size, initial diagnosis, age, sex, demographics).

Risk of bias in individual studies and quality assessment
Two authors (JH and MW) independently assessed studies for bias using a modified Quality Assessment Tool for Quantitative Studies, originally developed by the Effective Public Health Practice Project. Any disagreement was resolved by discussion with a third author (SW). Quality of studies was assessed across several domains including selection bias, study design, confounders, data collection method, and withdrawals and dropouts. The scores were collated to give an overall global rating for each paper as “Strong”, “Moderate” or “Weak”. If a study received a weak rating in all areas of bias, it was excluded from the review.

Synthesis of results and meta-analysis
A mixed-methods quantitative and narrative synthesis was carried out due to the small number of studies and heterogeneity in study methodology.

In terms of the quantitative analyses, the percentage of change in diagnoses, diagnostic confidence and management was computed using available study data. A random-effects meta-analysis was conducted to calculate pooled estimates of the percentage change in diagnoses, confidence and management, due to the heterogeneity in study settings and study populations. Subanalyses were performed on the percentage change in AD diagnoses, that is, changes in diagnosis from AD to non-AD and from non-AD to AD. The I^2 statistic was used to assess the degree of heterogeneity of the percentage change in diagnosis, confidence and management across studies. We followed Tu’s 2016 methodology for testing the relationship between percentage change and baseline values, which uses a modified Pearson’s test. All analyses were performed using R Software R V.4.1.2; R Foundation for Statistical Computing.

RESULTS
Study identification
Seventeen studies were identified for inclusion. The PRISMA flowchart is displayed in figure 1. In total, 5816 records were identified from 4 databases; Medline, Embase, PsycINFO and Web of Science. After removal of duplicates, 3071 records were screened; 3031 records were excluded. Reasons for exclusion included not relevant to diagnosis of dementia, did not involve relevant CSF markers and explored analytical validity of CSF markers. Forty reports were assessed for eligibility. Twenty-three reports were excluded. Reasons for exclusion were poster abstracts, study protocols, not in English, no exact data, review or similar and study of clinical utility of blood biomarker.

Study characteristics
Study characteristics are shown in table 1 and table 2 and in online supplemental table 2.
<table>
<thead>
<tr>
<th>Author, year of Publication</th>
<th>Country</th>
<th>Type of study</th>
<th>Referral setting</th>
<th>Intervention</th>
<th>Study duration</th>
<th>Patient sample size (N)</th>
<th>Clinician sample size (N)</th>
<th>Patient inclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balasa et al, 2013</td>
<td>Spain</td>
<td>Prospective observational study</td>
<td>Specialist outpatient clinic</td>
<td>LP for CSF biomarkers: Aβ42, t-tau and p-tau</td>
<td>2009–2013</td>
<td>157</td>
<td>NR</td>
<td>Patients &lt;65 years</td>
</tr>
<tr>
<td>Boelaarts et al, 2020</td>
<td>The Netherlands</td>
<td>Prospective observational study</td>
<td>Community geriatric outpatient clinic</td>
<td>LP for CSF biomarkers: Aβ42, t-tau and p-tau</td>
<td>2010–2016</td>
<td>69</td>
<td>NR</td>
<td>Patients &lt;71 years</td>
</tr>
<tr>
<td>Duits et al, 2015</td>
<td>The Netherlands</td>
<td>Prospective observational study</td>
<td>Memory clinic</td>
<td>LP for CSF biomarkers: Aβ42, t-tau and p-tau</td>
<td>2011–2012</td>
<td>351</td>
<td>5</td>
<td>All patients visiting the clinic</td>
</tr>
<tr>
<td>van den Brink et al, 2020</td>
<td>Canada</td>
<td>Retrospective observational study</td>
<td>Specialist memory clinic</td>
<td>LP for CSF biomarkers: Aβ42, t-tau, and p-tau and FDG-PET</td>
<td>2017–2019</td>
<td>28</td>
<td>NR</td>
<td>Atypical dementia presentations</td>
</tr>
<tr>
<td>Falgàs et al, 2019</td>
<td>Spain</td>
<td>Prospective observational study</td>
<td>Specialist memory clinic</td>
<td>Patients underwent biomarkers which included MRI, LP for CSF biomarkers: Aβ42, t-tau and p-tau, FDG-PET, amyloid PET</td>
<td>Not reported</td>
<td>40</td>
<td>5</td>
<td>&lt;65 years of age, MMSE score ≥18</td>
</tr>
<tr>
<td>Gjerum et al, 2021</td>
<td>Denmark</td>
<td>Retrospective observation incremental study</td>
<td>Memory clinic</td>
<td>Patients randomised to addition of either 2-[18F]FDG-PET or CSF biomarkers: Aβ42, t-tau and p-tau</td>
<td>2015–2016</td>
<td>81</td>
<td>2</td>
<td>Cognitive impairment due to neurodegenerative disease (MMSE≥18, CDR≥1.0, undergone T1-weighted MRE≥1.5 T, addition of CSF biomarkers deemed useful by clinician)</td>
</tr>
<tr>
<td>Gooblar et al, 2015</td>
<td>USA</td>
<td>Study using simulated clinical vignettes</td>
<td>Primary, secondary and tertiary centres</td>
<td>Simulated CSF values</td>
<td>January–July 2013</td>
<td>2</td>
<td>193</td>
<td>2 Simulated clinical vignettes</td>
</tr>
<tr>
<td>Handels et al, 2017</td>
<td>The Netherlands</td>
<td>Cost-effectiveness analysis</td>
<td>NA</td>
<td>Simulated CSF values</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Simulated patients with MCI</td>
</tr>
<tr>
<td>Kester et al, 2010</td>
<td>The Netherlands</td>
<td>Prospective observational study</td>
<td>One local hospital memory clinic</td>
<td>LP for CSF biomarkers: Aβ42, t-tau and p-tau</td>
<td>2005–2008</td>
<td>109</td>
<td>2</td>
<td>All patients visiting the clinic</td>
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<tr>
<td>Lee et al, 2017</td>
<td>Canada</td>
<td>Cost-effectiveness analysis</td>
<td>NA</td>
<td>Simulated CSF values</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Simulated patients with suspected AD</td>
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<tr>
<td>Mouton-Liger et al, 2014</td>
<td>France</td>
<td>Prospective observational study</td>
<td>secondary or tertiary memory centres</td>
<td>LP for CSF biomarkers: Aβ42, t-tau and p-tau</td>
<td>Not specified</td>
<td>561</td>
<td>128</td>
<td>When a clinician considered a patient eligible for CSF biomarkers</td>
</tr>
<tr>
<td>Paquet et al, 2016</td>
<td>France</td>
<td>Prospective observational study</td>
<td>29 Secondary and tertiary memory clinics</td>
<td>LP for CSF biomarkers: Aβ42, t-tau and p-tau</td>
<td>2014–2016</td>
<td>69</td>
<td>128</td>
<td>Initial main diagnosis of a psychiatric disorder</td>
</tr>
<tr>
<td>Ramusino et al, 2019</td>
<td>Italy</td>
<td>Prospective study</td>
<td>Multicentre, 4 memory clinics</td>
<td>LP for CSF biomarkers: Aβ42, t-tau and p-tau and amyloid-PET</td>
<td>2015–2017</td>
<td>71</td>
<td>2</td>
<td>MCI or mild dementia possibly due to AD, age range 55–90 years, score &lt;4 on the modified Hachinski ischemic scale At least 5 years of education</td>
</tr>
</tbody>
</table>
### Table 1 Continued

<table>
<thead>
<tr>
<th>Author, year of Publication</th>
<th>Country</th>
<th>Type of study</th>
<th>Referral setting</th>
<th>Intervention</th>
<th>Study duration</th>
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<th>Clinician sample size (N)</th>
<th>Patient inclusion criteria</th>
</tr>
</thead>
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<tr>
<td>Stiffel et al, 2021</td>
<td>Canada</td>
<td>Prospective observational study</td>
<td>A tertiary care memory clinic</td>
<td>LP for CSF biomarkers: Aβ42, t-tau and p-tau</td>
<td>2015–2020</td>
<td>262</td>
<td>NR</td>
<td>Participants included if basic tertiary care work-up, neuropsychological evaluation and FDG-PET did not provide conclusive diagnosis</td>
</tr>
<tr>
<td>Valcárcel-Nazco et al, 2014</td>
<td>Spain</td>
<td>Cost-effectiveness analysis—economic evaluation</td>
<td>NA</td>
<td>Simulated CSF values</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Simulated patients with MCI and other dementias</td>
</tr>
<tr>
<td>Ye et al, 2021</td>
<td>China</td>
<td>Prospective observational study</td>
<td>Neurology clinic</td>
<td>LP for CSF biomarkers: Aβ42, t-tau and p-tau</td>
<td>2015–2019</td>
<td>137</td>
<td>Not reported</td>
<td>All patients visiting the clinic</td>
</tr>
</tbody>
</table>

AD, Alzheimer's disease; Aβ42, amyloid beta 42; CDR, Clinical Dementia Rating; CSF, cerebrospinal fluid; FDG-PET, fluorodeoxyglucose positron emission tomography; LP, lumbar puncture; MMSE, Mini Mental State Examination; NR, not reported; P-tau, phospho-tau; T-tau, total tau.

### Quality assessment

Most (11 of 17, 65%) studies were assessed as being of moderate quality.42–44 Two studies were assessed as being of high quality,45 46 and three studies were assessed as being of low quality.47 48 No studies were assessed as being of high quality.49 50 Only three studies were assessed as being of moderate quality.42–44 Two studies were assessed as being of high quality,45 46 and one study was assessed as being of low quality.47 48

### Outcome measures

Outcome measures are described in online supplemental table 2. The majority (13 of 17, 76%) of studies restricted the clinician to complete a pre-CSF and post-CSF results questionnaire, while listing initial and final diagnoses, respectively.30–34 36–41 46 47 Of these studies, eight examined the ability of fluid biomarker results to change diagnostic confidence,32–36 40 41 46 47 and seven assessed the impact of CSF biomarker results on patient management, defined as the initiation or discontinuation of dementia medications such as cholinesterase inhibitors, the ability to enrol in clinical trials, and/or length of time costs and quality-adjusted life-years (QALYs).42 43

Most studies recruited clinicians with a specialty in Neurology, but only one study provided detailed clinician demographics.41

### Findings

#### Changes in diagnosis

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Most studies recruited clinicians with a specialty in Neurology, but only one study provided detailed clinician demographics.41
The change in confidence was inversely proportional to the overall pooled percentage change in diagnoses was 25% (95% CI 14 to 37) and there was substantial heterogeneity (I² 97%, p<0.001) (figure 2a). Subgroup analyses found no significant change in diagnoses from initial AD to final non-AD or initial non-AD to final AD (online supplemental figures1A and B).

Two studies explored the accuracy of clinicians’ final diagnoses through longitudinal patient follow-up. In one study, after 12 months of follow-up, 89% of patients’ diagnoses were found to be correctly classified. Similarly, another study showed that after a mean follow-up time of 31 months, 88% of AD participants maintained their diagnosis and all MCI participants who had positive CSF results progressed to AD dementia.

Clinician-rated diagnostic confidence

Eight studies calculated and showed an overall increase in diagnostic confidence, ranging from 5% to 22% (online supplemental table 2). The overall pooled percentage change in confidence was 14% (95% CI 9 to 18) and there was substantial heterogeneity (I² 88%, p<0.001) (figure 2b).

The change in confidence was inversely proportional to the initial pre-test confidence level, such that lower pre-test confidence was associated with a greater percentage change in confidence (Pearson’s r = −0.91, p<0.001).

Two studies that reported an overall increase pooled percentage change in confidence also showed a decrease in diagnostic confidence for a minority of clinicians. This was often associated with patients for whom CSF results did not alter the final diagnosis and who had a pre-biomarker diagnosis of subjective memory complaint or a psychiatric disorder.

Change in management

Five studies, comprising 918 patients, evaluated the impact on CSF biomarkers on patient management. The overall proportion of patients whose management changed after availability of fluid biomarkers ranged between 13% and 47%, and the overall pooled proportion of patients whose management changed was 31% (95% CI 12 to 50) with substantial heterogeneity (I² 97%, p<0.001) (figure 2c). The most common management change was the commencement or stopping of cholinesterase inhibitors or other dementia medications (four of five studies).

Cost-effectiveness

Three studies analysed the cost-effectiveness of CSF biomarkers to diagnose AD in MCI and dementia populations: a 2014 Spanish study and two studies published in 2017 from Canada and The Netherlands. All three studies assessed CSF biomarkers as an alternative, less expensive and more efficient diagnostic tool compared with standard clinical diagnostic criteria. The same study reported that for patients with dementia, despite higher uncertainty, CSF biomarkers were also a cost-effective alternative compared with standard clinical diagnostic criteria.

A second study used a Markov model to estimate the lifetime costs and QALYs of CSF biomarkers in patients referred

<table>
<thead>
<tr>
<th>Author, year of publication</th>
<th>Type of study</th>
<th>Aim</th>
<th>Outcome measure</th>
<th>Statistical analysis</th>
<th>Summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Handels et al, 2017 The Netherlands</td>
<td>Cost-effectiveness analysis</td>
<td>To estimate the potential ICER of adding CSF biomarker testing to the standard diagnostic work-up to determine the prognosis for patients with MCI</td>
<td>Accuracy of prognosis</td>
<td>Simulated data model using a merged dataset</td>
<td>Improved the accuracy of prognosis by 11%</td>
</tr>
<tr>
<td>Lee et al, 2017 Canada</td>
<td>Cost-effectiveness analysis</td>
<td>To estimate the lifetime costs and QALYs of CSF biomarker analysis in a cohort of patients referred to a neurologist or memory clinic with suspected AD who remained without a definitive diagnosis of AD or another condition after neuroimaging</td>
<td>Additional cost per patient</td>
<td>Markov model</td>
<td>AD pre-test probability of 12.7%; average QALY gain of 0.015/ICER of €113.02 per QALY gained €1.165 additional costs per patient</td>
</tr>
<tr>
<td>Valcárcel-Nazco et al, 2014 Spain</td>
<td>Cost-effectiveness analysis—economic evaluation</td>
<td>To determine the cost-effectiveness of the CSF biomarkers to diagnose AD in patients with MCI and those with dementia</td>
<td>Cost and effectiveness</td>
<td>Probabilistic sensitivity analysis using 2nd-order Monte Carlo simulations. Acceptability curves were calculated and ANCOVA models applied to simulation results</td>
<td>Patients with MCI: lower average cost per patient of €1832.65. Patients with AD: higher average cost per patient of €1133.82. Dominant ICER for patients with MCI</td>
</tr>
</tbody>
</table>

AD, Alzheimer’s disease; ANCOVA, analysis of covariance; CSF, cerebrospinal fluid; ICER, incremental cost-effectiveness ratio; MCI, mild cognitive impairment; QALY, quality-adjusted life year.
was no difference in terms of added diagnostic value between them, with no apparent benefit of using another biomarker if amyloid-PET or CSF biomarkers had been performed. However, in another study, amyloid-PET provided greater changes in diagnosis and diagnostic confidence than CSF biomarkers. For participants correctly diagnosed as patients with AD, CSF biomarkers had a significantly higher impact on diagnostic and a significant reduction in the need for further investigations when compared with FDG-PET. One study reported that for 35% of patient participants, FDG-PET and CSF-based diagnosis did not correspond.

DISCUSSION

Previous systematic reviews have reported on the analytical or clinical validity of fluid biomarkers, or the clinical utility of imaging biomarkers such as amyloid-PET. In this review, we focused specifically on the clinical utility of CSF biomarkers in the assessment of patients with cognitive impairment and the cost-effectiveness of CSF biomarkers for AD.

Use of CSF biomarkers resulted in a change in diagnosis in 25% of cases, although this was not specific to any direction of diagnostic change (AD to non-AD or non-AD to AD). This result is similar to the overall change of diagnosis of 35.2% after amyloid-PET.

Biomarker results are likely to provide an additional diagnostic assessment tool that clinicians will consider in combination with clinical findings. In one study that provided simulated clinical vignettes to clinicians, an AD clinical presentation with AD CSF results led to a significantly increased odds of an AD diagnosis, whereas when clinicians were given borderline CSF values, they relied on other clinical information to decide on the final diagnosis. Also, when clinicians were shown a mild AD clinical presentation with normal CSF results, they often chose a diagnosis of unknown aetiology, and when clinicians were shown an ambiguous clinical presentation with AD CSF result, they were more likely to make an AD diagnosis.

Studies consistently reported that CSF biomarkers improved clinicians’ diagnostic confidence with a pooled mean increase of 14%. This is in comparison with the impact of amyloid-PET where the change in confidence level reportedly ranged from 16% to 44%. However, some studies reported that biomarker results resulted in a reduction in confidence, for example, in the context of unexpected biomarker results when patients with subjective cognitive complaint or a psychiatric disorder had abnormal dementia biomarkers, or when patients initially diagnosed with AD had normal biomarkers. It is relevant that higher diagnostic confidence may not always equate to greater clinical utility, as decreased confidence after CSF results could sometimes help a clinician to question their pre-CSF diagnosis and prevent an incorrect diagnosis. A reduction in diagnostic confidence may also spur further diagnostic tests and have a substantial impact on management.

Use of CSF biomarkers led to a change in management in 31% of cases, mostly involving the initiation or discontinuation of cholinesterase inhibitors. One review examining the impact of amyloid-PET found that the overall change in management was 59.6%, which represents a larger pooled effect size compared with CSF biomarkers. This may be due to factors such as the proportion of patients already prescribed medication and degree of diagnostic certainty prior to amyloid-PET imaging.

Cost-effectiveness analyses
revealed CSF biomarkers to be a cost-effective alternative to standard diagnostic work-up.\textsuperscript{42-44} There was conflicting evidence regarding the utility of CSF biomarkers in addition to specialist imaging including FDG-PET and amyloid-PET.

Despite the findings in this review, there is low utilisation of CSF biomarkers in memory services in the UK, where staff do not have access to the specialist equipment and expertise to perform routine LPs. There have been recent advancements in the validation of blood-based biomarkers, such as ptau-181 and ptau-217, which have been shown to have similar sensitivity and specificity to CSF biomarkers.\textsuperscript{53} In one prospective observational study, serum neurofilament light was perceived as a useful additional tool to CSF biomarkers in 53\% of cases by neurologists in a tertiary memory clinic.\textsuperscript{37} In a recent position statement, serum neurofilament light was perceived as a useful biomarker in memory clinics as part of the diagnostic work-up of patients with cognitive symptoms, with the results confirmed where possible with CSF biomarkers and amyloid PET imaging.\textsuperscript{54} Further studies are needed to establish if the clinical utility of blood-based biomarkers is comparable with CSF biomarkers and amyloid PET imaging. Blood-based biomarkers are simple to carry out and cost-effective.\textsuperscript{16} They could be made widely available and have the potential to be used within UK memory services to support the diagnosis of Alzheimer’s dementia.

In the UK, there is a lack of information on the investigation and management of MCI in the NICE guidelines.\textsuperscript{35} It would be important to address this in future guidance, given the increasing proportion of people diagnosed as MCI in UK memory services.\textsuperscript{36}

Limitations

The interpretation of the findings is limited by the small number of included studies, small sample sizes and high methodological heterogeneity. Most included studies were of moderate quality. Study quality limitations included lack of information about baseline clinician demographics and were observational studies. Only one study reported on clinician demographics such as ethnicity, age and level of seniority, and most clinicians were neurologists, so it is unknown how these clinician factors may have influenced the outcome measures, such as degree of diagnostic confidence and familiarity with the use of fluid biomarkers. The extent to which these findings are generalisable to other clinician specialties involved in making dementia diagnoses is also unclear.

Most studies include a population of mainly white and well-educated participants. In future studies, it will be important to investigate the use of CSF biomarkers in more diverse populations. The mean age of patients included in these studies was 66.1 years. Future studies should investigate older patients, who are more representative of local memory service populations.

Some studies requested clinicians in Memory Services to complete questionnaires on a voluntary basis, which may have introduced a selection bias as clinicians with a higher inclination to use biomarkers and find them useful in clinical practice may have been more likely to respond.\textsuperscript{15,32}

No studies confirmed the final diagnosis with postmortem brain study findings, so we were unable to assess the overall diagnostic accuracy of fluid biomarkers. Future larger longitudinal studies would be helpful to assess the diagnosis accuracy of these methods.

Only one study assessed the clinical utility of a serum biomarker, sNfL, in the diagnosis of neurodegenerative diseases.\textsuperscript{43} Further studies are needed to assess the clinical impact of other blood-based biomarkers.

Conclusion

CSF biomarkers provide additional value in the diagnostic assessment of cognitively impaired patients presenting to memory clinic through changes in clinical diagnoses, improved diagnostic confidence and changes to patient management. Large multicentre studies have shown LP to be a safe and tolerated procedure. In the future, fluid biomarkers, especially blood-based biomarkers, offer a simple-to-obtain, cost-effective and scalable test to support clinicians in the diagnosis of Alzheimer’s dementia.

Contributors

All authors contributed to the conception and design of the review. MW and JH completed the data collection. JH and KYL performed the data analysis and interpretation. All authors contributed to drafting of the article, revision of the article and final approval of the version to be published.

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Patient consent for publication

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Ethics approval

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Provenance and peer review

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Supplemental material

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REFERENCES

Neurodegeneration


