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Cost-effectiveness comparison between blood biomarkers and conventional tests in Alzheimer's disease diagnosis

Kenta Noda [1], Yeongjoo Lim [2], Rei Goto [3], Shintaro Sengoku [4], Kota Kodama [1,2,5,6,*]

Dementia management has evolved with drugs such as lecanemab, shifting management from palliative care to early diagnosis and intervention. However, the administration of these drugs presents challenges owing to the invasiveness, high cost and limited availability of amyloid-PET and cerebrospinal fluid tests for guiding drug administration. Our manuscript explores the potential of less invasive blood biomarkers as a diagnostic method, with a cost-effectiveness analysis and a comparison with traditional tests. Our findings suggest that blood biomarkers are a cost-effective alternative, but with lower accuracy, indicating the need for multiple specific biomarkers for precision. This underscores the importance of future research on new blood biomarkers and their clinical efficacy.

Keywords: Pharmacogenomics; Next-generation sequencing; Population group; Biomarkers

Introduction

Alzheimer's disease (AD), the most common form of dementia, has a major impact on global public health. An important pathological feature of AD is the accumulation of β-amyloid peptide (Aβ) in the brain,[(p1)] with mild symptoms such as a decline in cognitive function beginning approximately 20 years before the onset of more severe symptoms.[(p2)] Therefore, the early detection of amyloid pathology is important for the diagnosis of AD and facilitates the enrollment of patients in clinical trials for this disease. Until recently, the treatment of dementia primarily relied on palliative care. However, with the approval of disease-modifying drugs such as aducanumab and lecanemab,[(p3)] there has been a paradigm shift in dementia management. Lecanemab has received full approval in the United States and has been the subject of regulatory applications in various countries, including Japan, where it was granted approval in August 2023. Currently, patient selection for lecanemab administration is determined through amyloid-PET and cerebrospinal fluid (CSF) tests, and lecanemab has been strategically designed for early-stage patients.

Harmful Aβ plaque accumulation can compromise nerve cell functionality, leading to significant damage.[(p4)] As a result, a focus on early diagnosis and swift therapeutic intervention is critical. Amyloid-PET and CSF biomarkers are now widely accepted research tools used to assess the Aβ status[(p5),(p6)] for AD diagnoses, as they reflect the disease state and are considered effective for making decisions on drug administration and monitoring the effects of the drug. However, amyloid-PET and

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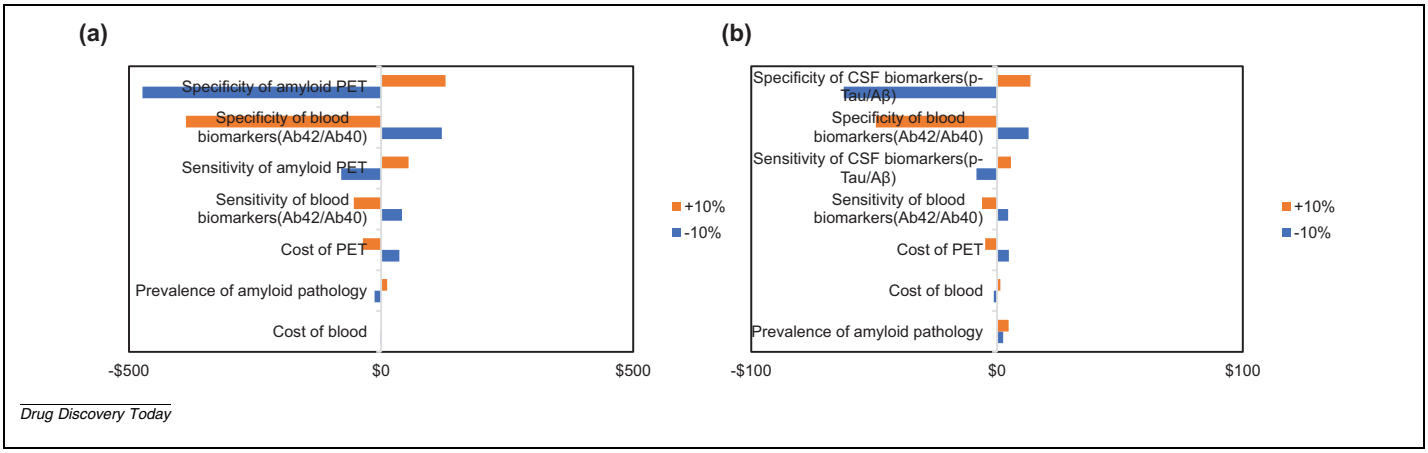

FIGURE 1

One-way deterministic tornado plot. The orange bars represent the effect on the ICER at +10% of the base and blue bars at −10% of the base. **(a)** Comparison between amyloid-PET and blood biomarkers; **(b)** the relationship between CSF and blood biomarkers.

CSF tests are invasive and expensive and are not universally available, which limits their use in routine clinical practice.[(p7),(p8)] Therefore, there is a need for tests which overcome these challenges, and numerous studies have investigated possible biomarkers for AD,[(p9)] particularly blood biomarkers, which can be measured in a relatively non-invasive and cost-effective manner.[(p10)] Clinical assessments of blood biomarker tests are still ongoing, and evidence of their efficacy is accumulating.

Cost-effectiveness analyses related to pharmaceuticals, including the new drug aducanumab, have been conducted in various contexts. In such analyses, factors such as the presence or absence of administration and target groups are considered. Furthermore, calculating the incremental cost-effectiveness ratio (ICER) by categorizing each treatment in detail has become standard practice.[(p11)] Recently, the use of established variance analysis to calculate the quality-adjusted life years and willingness to pay (WTP) has become standardized across various drugs and diseases.[(p12)]

When it comes to diagnostics, however, there have been very few reports that consider their cost-effectiveness in terms of clinical performance and the cost of implementing new tests in clinical practice. Among these, Contador *et al*. reported on the cost-effectiveness of amyloid-PET compared with AD lumbar puncture biomarkers. They adopted the ICER to measure the cost per percentage of correct diagnoses detected and indicated that amyloid-PET is not a cost-effective technique when compared with AD CSF biomarkers.[(p13)] Moreover, there have been no reports on the cost-effectiveness of blood biomarkers, a recent trend in testing.

Therefore, we examined the cost-effectiveness of blood biomarker tests in comparison with amyloid-PET and CSF tests, with the aim of elucidating the parameters that influence the cost-effectiveness of blood biomarkers. We specifically focused on the United States, the first country to approve lecanemab, because we assumed that this country is the most likely to have advanced research on the diagnoses necessary for administering lecanemab and the related biomarkers. This study will provide guidance for the development of blood biomarkers and their implementation in clinical settings.

Model inputs

The published literature was used to inform the model. The input data included the prevalence, sensitivity and specificity of the biomarkers (Table 1).[(p14),(p15),(p16),(p17),(p18)] When inputting different data into a model, it is assumed that the bias will be minimized if the same cohort set is used for each marker. Therefore, we chose the Alzheimer's Disease Neuroimaging Initiative (ADNI) study as the cohort set used in each test. The ADNI has made a global impact, first by developing a set

TABLE 1

Model inputs				
Item	**Base**	**−10%**	**10%**	**Refs**
Prevalence of amyloid pathology	22.80%	20.52%	25.08%	(p14)
Sensitivity of amyloid-PET	88%	79%	97%	(p15)
Specificity of amyloid-PET	81%	73%	89%	(p15)
Sensitivity of CSF biomarkers (p-Tau/Aβ)	83%	75%	91%	(p15)
Specificity of CSF biomarkers (p-Tau/Aβ)	81%	73%	89%	(p15)
Sensitivity of blood biomarkers (Ab42/Ab40)	64%	58%	70%	(p16)
Specificity of blood biomarkers (Ab42/Ab40)	74%	67%	81%	(p16)
Cost of PET	$3,935.37	$3,541.83	$4,328.91	(p17)
Cost of CSF	$468.28	$421.45	$515.11	(p17)
Cost of blood	$130.00	$117.00	$143.00	(p18)

of standardized protocols to allow for comparisons of results from multiple centers. To date, more than 1,000 scientific publications have used ADNI data. Many other initiatives related to AD and other diseases have been designed and implemented using ADNI as a model.[p19] In addition, the blood biomarker used for the model input in this study was confirmed to exhibit no significant differences in clinical performance, even with other large cohorts. We referenced previous studies and extracted the sensitivity and specificity of each test performance evaluated using the ADNI cohort as input information.[p13] The measure of effectiveness was the percentage of appropriately diagnosed cases. Therefore, no additional costs or effects were considered. We also determined the false positives, false negatives, true positives and true negatives from the specificity and sensitivity of each diagnostic method.[p13] Accuracy was determined using Equation (1):

$$\begin{aligned}\text{Accuracy} = {} & \text{true positive rate} \\ & (\text{AD}^{+}\text{and diagnosis positive}) \\ & + \text{ true negative rate} \\ & (\text{AD}^{-}\text{and diagnosis negative}) \quad (1)\end{aligned}$$

Sensitivity analysis

One-way sensitivity analysis and probabilistic sensitivity analysis were used to analyze the uncertainty around the model inputs. In general, the uncertainty component of the analysis varies by 10% relative

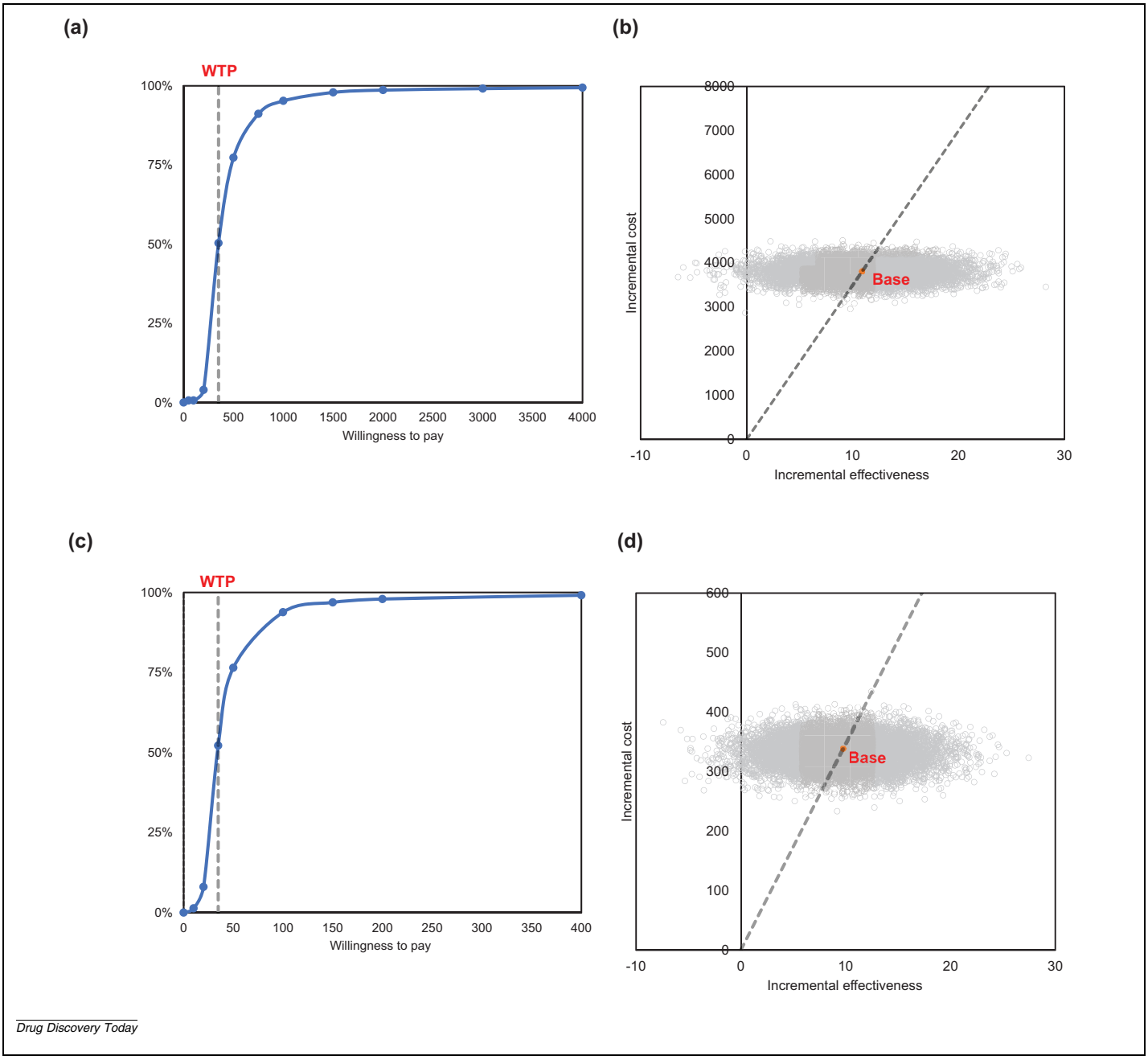

FIGURE 2

Incremental cost-effectiveness plane and probabilistic sensitivity analyses (Monte Carlo simulations). **(a,b)** Comparison of amyloid-PET and blood biomarkers. **(c,d)** Comparison of CSF and blood biomarkers.

to the base value. In unidirectional determinism, tornado plots show the influence of each parameter. A probabilistic sensitivity analysis was performed using Monte Carlo simulations with 10,000 iterations. One-way sensitivity and probabilistic sensitivity analyses were performed using Microsoft Excel for Microsoft 365 MSO. Monte Carlo simulations were performed to generate random variations using RStudio (ver. 2023.06.2+561) with the normal distribution set to 95%, and each base value was the average value. R was used because of its high reliability in generating random numbers. The parameters included the prevalence of patients with AD and the sensitivity, specificity and cost of each diagnosis. All visualizations were performed using Microsoft Excel for Microsoft 365 MSO.

Accuracy of each diagnosis and base case

To test costs, we used those not covered by insurance in the United States. The accuracies of the amyloid-PET, CSF and blood biomarker tests were 82.60, 81.46 and 71.72, respectively. The incremental cost of amyloid-PET and blood biomarkers was $3,805.37, and the incremental accuracy of the diagnosis was 10.88. In this case, the ICER was calculated as $349.89, which indicates the WTP for amyloid-PET. The incremental cost of CSF and blood biomarkers was $338.28, and the incremental accuracy of diagnosis was 9.74. In this case, the ICER was calculated as $34.75, which indicates the WTP for CSF.

One-way sensitivity analysis

As shown in Figure 1a, the amyloid-PET specificity had a greater impact on cost-effectiveness than the specificity of the blood biomarkers. The specificity of the blood biomarkers had a major role in this evaluation. Both amyloid-PET and blood biomarkers had a low impact on the cost. When comparing blood and CSF biomarkers, the specificity of blood biomarkers had the greatest impact on cost-effectiveness, followed by CSF biomarkers (Figure 1b). Both CSF and blood biomarkers had a low impact on cost.

Probabilistic sensitivity analysis

For probabilistic sensitivity analysis, we estimated the distribution of the effects and costs of blood biomarkers and existing tests and evaluated the probability that the ICER falls below a certain WTP. In addition, we created a cost-effectiveness acceptability curve by displaying these evaluation results on a graph. Figure 2a,b shows a comparison between amyloid-PET and blood biomarkers. The acceptance probability was more than 90% with a WTP of $1,000, as shown in Figure 2a. The acceptance probability increased sharply from $300 and reached a plateau at $750. In the base case, for the WTP, the acceptance probability at $349.89 was 50.4%. A comparison of CSF and blood biomarkers is shown in Figure 2c,d. An acceptance probability of more than 90% corresponds to a WTP of more than $100. The acceptance probability increased sharply from $30 and reached a plateau at $100. The acceptance probability at $34.75 was 52.2%.

Discussion

For AD, various cost–benefit analyses have been conducted in relation to therapeutic medications, considering the comprehensive quality of life, inclusive of disease progression. Because the cost of medication is very high, it is important to select the right patients for treatment. Therefore, it is necessary to improve the diagnostic accuracy to select a group for which the drug is more effective. In this study, we focused on diagnostic accuracy, because with the advent of therapeutics, the presence or absence of diagnostic administration significantly contributes to the quality of life and costs thereafter.[p20] Therefore, a focus on diagnostic accuracy requires a cost-effectiveness analysis for the test, which should be well below the WTP for the medication. Furthermore, the primary issue is the lack of descriptions of test accuracy in terms of cost-effectiveness. This should be considered not only for AD but also for cancer, especially for expensive molecular targeted drugs, such as immune checkpoint inhibitors.[p21]

CSF tests obtained from lumbar puncture or imaging technology have been commonly used in AD diagnoses.[p7] The performance of blood biomarkers has been compared with that of amyloid-PET and CSF biomarkers, with the agreement with control reports being analyzed on the basis of the area under curve, and the clinical usefulness of blood biomarkers has been evaluated.[p22] Because blood biomarkers provide limited direct evidence for an AD diagnosis, they might serve as a screening tool to decide whether to conduct more established diagnostic tests.

In anticipation of the direct diagnosis of AD using blood biomarkers in the future, we conducted a cost-effectiveness analysis. A one-way sensitivity analysis was performed to determine which parameters had the most impact. Comparing conventional tests with blood biomarkers, the specificity of the test had the highest impact on the ICER, and the cost had the lowest impact (Figure 2). These results suggest that research on more disease-specific tests will continue to be pursued, and new and more expensive tests are likely to be accepted. In addition, the results of a probabilistic sensitivity analysis comparing conventional tests and blood biomarkers only yielded an approximate 50% acceptance probability in terms of the WTP for both comparisons. This implies that it might be difficult for current tests to gain acceptance from customers, such as patients or doctors, owing to their poor cost-effectiveness compared with that of blood biomarkers. However, amyloid-PET resulted in more than 90% acceptance at a WTP of more than $1,000 when compared with blood biomarkers. At a WTP of $1,000, this indicates a margin of approximately eight times that of the assumed blood biomarker measurement cost of $130. These results suggest the potential for setting a higher cost for blood biomarkers and also indicate the possibility of combining multiple blood biomarkers.

However, a comparison with CSF showed an acceptable result of more than 90% for a WTP of more than $100. In this case, the cost difference is not very large, and thus adding a blood biomarker would be difficult. However, lumbar puncture is painful and side effects such as fever and numbness of the hands and feet have been reported.[p23] In the worst cases, a risk of microbiological infection of the wound has also been reported, but in reality, such events are rare, and the results obtained from lumbar punctures in diagnosed patients are important. The awareness of lumbar puncture also largely depends on the country, and some patients have been reported to question or refuse the procedure.[p24] Blood tests, however, are consid-

ered more acceptable as general tests because they are less invasive. Whereas blood biomarkers present a lower-cost alternative to conventional tests for AD, they pose a challenge owing to their lower specificity (Table 1).

Research on blood biomarkers that aims to address this issue is a trend in the AD field, and efforts are being made to classify markers according to patient conditions and to explore and study markers with a higher accuracy to obtain more precise diagnostic results. Dementia is a multifactorial process, and Jack *et al.* defined blood biomarkers as biological components of AD and as signifiers of events that lead to cognitive impairment. Biomarkers have been grouped into β-amyloid deposition, pathological tau and neurodegeneration biomarkers (ATN biomarkers) according to the pathological process that each one measures.[p25] There is potential to improve diagnostic accuracy by correlating a specific combination of blood biomarkers to a specific disease state.

In this study, we used immunological assays for biomarker proteins and peptides as model inputs.[p26] These assays have been extensively researched, but other methodologies for molecular detection have been similarly well studied, including genetic testing for biomarkers such apolipoprotein E4 (*ApoE4*)[p27] and mass spectrometry.[p26] It is likely that diagnoses that combine these methods will show higher accuracy; however, recent improvements in analytical performance, such as increased sensitivity, have meant that each method now shows very good clinical performance even on its own. Therefore, the focus should be on research into biomarkers rather than improvements in methodologies.

The results of our study suggest that test costs have little effect on the ICER, implying the potential for expanding the range of blood biomarker tests. Therefore, the advancement of research on various biomarkers, including the ATN classification that reflects the disease state, is crucial for improving diagnostic accuracy. In terms of diagnosis based on multiple biomarkers, genetic panel testing could be useful.

The limited discussion of diagnostic accuracy in the context of decision-making for drug administration significantly affects the feasibility and cost-effectiveness of drug treatments. This is not only crucial in the field of cancer, as demonstrated by San Miguel *et al.*,[p28] but also in our study on AD biomarkers. It is evident that the performance of biomarkers has a pivotal role in researching the cost-effectiveness of future drug treatments. When contemplating any intervention, including treatment, it is crucial to consider the accuracy of the diagnosis that identifies the target group. Although there are reports of improved specificity when tests for different biomarkers are combined, false positives might also occur if we cannot enhance the specificity of the tests for each biomarker. This could lead to unnecessary drug administration, potentially increasing the overall cost. Furthermore, the appropriate use of blood biomarkers, including the type of sample and its handling, is essential, underlining the importance of fostering an environment aimed at proper use.[p29] These points suggest that further verification is necessary before biomarker tests can be implemented in the real world. Moreover, it is important to consider these points when combining multiple biomarkers, factoring in the specificity of the biomarkers.

This study has some limitations. Specifically, the inputs used originated from a limited number of sources in the literature. Furthermore, we only focused on the clinical performance of each diagnosis and did not consider the analytical performance and appropriate use of each diagnostic test. Therefore, it is necessary to consider this information to create more robust data inputs. Moreover, the prices and diagnostic accuracy in this probability distribution analysis might differ from those in the real world, because the Monte Carlo simulation was performed assuming a normal distribution. Generally, biomarker data might not follow a normal distribution owing to influencing factors (such as age and sex). The Aβ used for the model input in this study is thought to exhibit a property close to a normal distribution, because it is less influenced by age, sex and other factors, and the result is from a cohort that incorporated samples in a strictly controlled environment. However, when evaluating new blood biomarkers, it is necessary to verify these variable and confounding factors.

In this study, we calculated the ICER on the basis of the accuracy and cost of the diagnosis. However, to verify the cost-effectiveness of the entire treatment for AD, a more detailed analysis (incorporating, for example, the quality-adjusted life years including the diagnostic flow) is necessary. Finally, even though the methodology has been reported in prior studies, it should be discussed whether customers would accept a WTP based on diagnostic accuracy.

Conclusions

This manuscript highlights two crucial points about blood biomarkers from the perspective of the ICER, and the specificity of these biomarkers should be the major consideration when selecting them. When considering the cost-effectiveness analysis of blood biomarkers, it was suggested that the implementation of multi-tests with added items could be a means to improve specificity. This study provides a direction for the development of acceptable blood biomarkers for real-world applications, and it might facilitate further advancements in this field.

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Declaration of interest

K.N. is an employee of the Sysmex Corporation. None of the other authors have any conflicts of interest related to the content of this article.

CRediT authorship contribution statement

Kenta Noda: Writing – original draft, Writing – review & editing, Data curation, Investigation, Methodology. **Yeongjoo Lim:** Supervision. **Rei Goto:** Supervision. **Shintaro Sengoku:** Supervision. **Kota Kodama:** Writing – review & editing, Supervision, Project administration.

Data availability

Data will be made available on request.

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References

1. Qiu C et al. Epidemiology of Alzheimer's disease: occurrence, determinants, and strategies toward intervention. *Dialogues Clin Neurosci*. 2009;11:111–128.
2. Scheltens P et al. Alzheimer's disease. *Lancet*. 2021;397:1577–1590.
3. van Dyck CH et al. Lecanemab in early Alzheimer's disease. *N Engl J Med*. 2023;388:9–21.
4. Chowdhury S, Chowdhury NS. Novel anti-amyloid-beta (Aβ) monoclonal antibody lecanemab for Alzheimer's disease: A systematic review. *Int J Immunopathol Pharmacol*. 2023;37 3946320231209839.
5. Petersen RC et al. Alzheimer's disease neuroimaging initiative (ADNI): clinical characterization. *Neurology*. 2010;74:201–209.
6. Shaw LM et al. Qualification of the analytical and clinical performance of CSF biomarker analyses in ADNI. *Acta Neuropathol*. 2011;121:597–609.
7. Milà-Alomà M et al. Latest advances in cerebrospinal fluid and blood biomarkers of Alzheimer's disease. *Ther Adv Neurol Disord*. 2019;12.
8. Thijssen EH et al. Highly specific and ultrasensitive plasma test detects Abeta(1–42) and Abeta(1–40) in Alzheimer's disease. *Sci Rep*. 2021;11:9736.
9. Noda K et al. Global biomarker trends in Alzheimer's research: A bibliometric analysis. *Drug Discov Today*. 2023;28 103677.
10. Pais MV et al. Plasma biomarkers of Alzheimer's disease: a review of available assays, recent developments, and implications for clinical practice. *J Alzheimers Dis Rep*. 2023;71:355–380.
11. Teramae F et al. Holistic cost-effectiveness analysis of anticancer drug regimens in Japan. *Drug Discov Today*. 2020;25:269–273.
12. Harty G et al. Consequences of biomarker analysis on the cost-effectiveness of cetuximab in combination with FOLFIRI as a first-line treatment of metastatic colorectal cancer: Personalised medicine at work. *Appl Health Econ Health Policy*. 2018;16:515–525.
13. Contador J et al. Cost-effectiveness of Alzheimer's disease CSF biomarkers and amyloid-PET in early-onset cognitive impairment diagnosis. *Eur Arch Psychiatry Clin Neurosci*. 2023;273:243–252.
14. Kern S et al. Prevalence of preclinical Alzheimer disease: comparison of current classification systems. *Neurology*. 2018;90:e1682–e1691.
15. Ben Bouallègue F et al. Comparison of CSF markers and semi-quantitative amyloid PET in Alzheimer's disease diagnosis and in cognitive impairment prognosis using the ADNI-2 database. *Alzheimers Res Ther*. 2017;9:32.
16. Tosun D et al. Detection of β-amyloid positivity in Alzheimer's Disease Neuroimaging Initiative participants with demographics, cognition, MRI and plasma biomarkers. *Brain Commun*. 2021;3: fcab008.
17. Tahami Monfared AA et al. Long-term health outcomes of lecanemab in patients with early Alzheimer's disease using simulation modeling. *Neurol Ther*. 2022;11:863–880.
18. Udeh-Momoh C et al. Blood derived amyloid biomarkers for Alzheimer's disease prevention. *J Prev Alzheimers Dis*. 2022;9:12–21.
19. Veitch DP et al. The Alzheimer's Disease Neuroimaging Initiative in the era of Alzheimer's disease treatment: a review of ADNI studies from 2021 to 2022. *Alzheimers Dement*. 2024;20:652–694.
20. Tahami Monfared AA et al. Estimated societal value of lecanemab in patients with early Alzheimer's disease using simulation modeling. *Neurol Ther*. 2023;12:795–814.
21. Aguiar PN Jr et al. The effect of PD-L1 testing on the cost-effectiveness and economic impact of immune checkpoint inhibitors for the second-line treatment of NSCLC. *Ann Oncol*. 2017;28:2256–2263.
22. Rissman RA et al. Plasma Aβ42/Aβ40 and phospho-tau217 concentration ratios increase the accuracy of amyloid PET classification in preclinical Alzheimer's disease. *Alzheimers Dement*. 2023. https://doi.org/10.1002/alz.13542.
23. Engelborghs S et al. Consensus guidelines for lumbar puncture in patients with neurological diseases. *Alzheimers Dement*. 2017;8:111–126.
24. Aldayel AY et al. Public knowledge and attitude toward lumbar puncture among adults in Riyadh, Saudi Arabia: a cross-sectional study. *SAGE Open Med*. 2019;7 2050312119871066.
25. Jack CR Jr et al. NIA-AA Research Framework: toward a biological definition of Alzheimer's disease. *Alzheimers Dement*. 2018;14:535–562.
26. Park SA et al. Promising blood biomarkers for clinical use in Alzheimer's disease: a focused update. *J Clin Neurol*. 2022;18:401–409.
27. Shang L et al. Association of APOE ε4/ε4 with fluid biomarkers in patients from the PUMCH dementia cohort. *Front Aging Neurosci*. 2023;15:1119070.
28. San Miguel L, Hulstaert F. The importance of test accuracy in economic evaluations of companion diagnostics. *J Comp Eff Res*. 2015;4:569–577.
29. Verberk IMW et al. Characterization of pre-analytical sample handling effects on a panel of Alzheimer's disease-related blood-based biomarkers: Results from the Standardization of Alzheimer's Blood Biomarkers (SABB) working group. *Alzheimers Dement*. 2022;18:1484–1497.

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