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Early detection of Alzheimer's disease: Progress, challenges, and future outlook

Alzheimer hastalığının erken teşhisi: Gelişmeler, zorluklar ve geleceğe bakış

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Abstract

Alzheimer's disease progressively impairs independence and memory, and no cure is currently available. Early diagnosis is crucial for slowing disease progression; however, existing interventions may pose risks, and standard diagnostic methods, such as brain imaging, lumbar puncture, and cognitive assessments, are often expensive, invasive, or inaccessible. Recent advances in blood biomarkers, including amyloid-beta and tau proteins, present a less invasive, more cost-effective, and scalable alternative. This review evaluates the validity, practicality, and limitations of current blood-based diagnostic tests for Alzheimer's disease. It addresses both technical challenges and ethical considerations, including equitable access and informed consent. The emergence of new treatments further underscores the importance of accurate and timely diagnosis. Although blood tests demonstrate significant potential for Alzheimer's diagnosis, their widespread adoption is constrained by requirements for improved accuracy, broader availability beyond specialized clinics, and adaptability to diverse healthcare environments. This review identifies strategies to enhance the scalability and accessibility of blood-based diagnostics and outlines subsequent steps for implementation. With continued technological and logistical advancements, blood-based tests could transform the landscape of Alzheimer's diagnosis.

Keywords: Alzheimer's disease, blood-based biomarkers, amyloid-beta, tau proteins, early diagnosis, diagnostic accessibility.

Özet

Alzheimer hastalığı, bireyin bağımsızlığını ve hafıza yetilerini giderek daha fazla kısıtlayan, ilerleyici bir hastalıktır ve şu an için kesin bir tedavisi bulunmamaktadır. Hastalığın ilerleyişini yavaşlatabilmek için erken teşhis hayati önem taşımaktadır. Ancak, mevcut müdahale yöntemleri çeşitli riskler taşıyabilirken, beyin görüntüleme, belden sıvı alma (lomber ponksiyon) ve bilişsel değerlendirmeler gibi standart teşhis yöntemleri de genellikle maliyetli, invaziv (girişimsel) ve her zaman erişilebilir değildir. Son dönemde kan biyobelirteçleri, özellikle de amiloid-beta ve tau proteinleri üzerine yapılan çalışmalar, bu sorunlara daha az invaziv, daha uygun maliyetli ve ölçeklenebilir bir alternatif sunmaktadır. Bu makale, Alzheimer hastalığı için mevcut kan bazlı teşhis testlerinin geçerliliğini, pratikliğini ve sınırlılıklarını değerlendirmektedir. Çalışmada hem teknik zorluklara hem de eşit erişim ve bilgilendirilmiş onam gibi etik konulara değinilmektedir. Yeni tedavilerin ortaya çıkışı, doğru ve zamanında teşhisin önemini daha da artırmaktadır. Kan testleri, Alzheimer teşhisinde büyük bir potansiyel barındırsa da, yaygın olarak benimsenmeleri önünde bazı engeller bulunmaktadır. Bunlar arasında daha yüksek doğruluk oranına ihtiyaç duyulması, bu testlerin sadece özel kliniklerle sınırlı kalmayıp daha geniş kitlelere ulaşması ve farklı sağlık hizmeti ortamlarına kolayca uyarlanabilmesi gerekliliği yer almaktadır. Bu derleme, kan bazlı teşhis yöntemlerinin ölçeklenebilirliğini ve erişilebilirliğini artırmaya yönelik stratejileri belirlemekte ve bunların uygulanması için atılması gereken adımları ortaya koymaktadır. Süregelen teknolojik ve lojistik gelişmelerle birlikte, kan testlerinin gelecekte Alzheimer hastalığı teşhisinde çığır açacağı öngörülmektedir.

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Anahtar kelimeler: Alzheimer hastalığı, kan temelli biyobelirteçler, amiloid-beta, tau proteinleri, erken teşhis, teşhis erişilebilirliği.

1. Introduction

Alzheimer's disease, the main cause of dementia, is quickly becoming one of the most expensive, deadly, and challenging health issues of our time [1]. Alzheimer's disease is a gradual decline in cognitive function that only shows symptoms after irreversible brain cell damage has already occurred [2]. Early detection of Alzheimer's disease (AD) changes its course, allowing for early treatment, future planning, and participation in clinical trials. Previously, an AD diagnosis relied on symptoms and was only confirmed after death by finding amyloid plaques and tau neurofibrillary tangles in the brain [3]. Nowadays, the diagnostic process has reached the stage of involving cognitive tests, neuroimaging techniques, and cerebrospinal fluid (CSF) biomarker assays, which add specificity; however, these approaches are typically hampered by their expense, invasiveness, and requirement for specialized equipment[4]. Nowadays, diagnosing Alzheimer's disease (AD) involves a few different methods. Cognitive tests like the Mini-Mental State Examination (MMSE) check for problems with memory and reasoning, but can't pinpoint the cause [5]. Neuroimaging techniques, such as MRI and amyloid PET scans, provide valuable information by showing brain shrinkage and the presence of amyloid plaques [6],[7]. Blood-based biomarker tests that have changed the paradigm of diagnosing AD are a new frontier. Tests measuring biomarkers associated with AD, such as amyloid-beta (Aβ) and tau, from a simple blood sample will likely increase access and uptake of AD-specific biomarkers into routine clinical practice. This review broadly speaks to the degree to which these tests may be relied on to detect AD in its early, preclinical phase, condemns their methodology underway currently, and weighs both potential benefits and drawbacks they pose. These technologies are highly promising, yet their implementation will depend on balancing fears regarding accuracy, scalability, and equity.

2. Current diagnostic methods

Typically, diagnosis of AD has relied on a combination of methods, which include clinical evaluations, neuropsychological tests, imaging methods, and biomarker-based techniques. Using these various methods for diagnosis allows for accurate identification of subjects, especially in early presentation. Here is a more thorough analysis of the necessary appraisal modalities for the diagnosis of AD:

2.1. Clinical and neuropsychological evaluations

Patient History and Clinical Evaluation: The assessment of Alzheimer's disease (AD) begins with a thorough patient history, typically obtained through direct interaction and supplemented by informant reports. These reports help gather information regarding cognitive impairment, behavioral changes, and functional decline. Both structured interviews and standardized evaluation tools support the evaluation of memory, language, visuospatial skills, and executive function

[7]. Evaluation is directed toward differentiating AD from other possible causes of cognitive impairment, such as vascular dementia or frontotemporal dementia. The National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria were originally published in 1984 and prescribe an initial clinical diagnosis, with progressive decline in memory as an important feature [7]. There have been numerous updates to this criterion since 1984 to enhance the use of biomarkers; however, both clinicians and researchers have relied upon the 1984 criteria as a framework for clinical practice [8].

2.2. Cognitive screening tools

Cognitive testing is an important aspect of cognitive screening and monitoring cognitive impairment in cases of AD and related dementias. A brief screening tool, MMSE, can be used to assess cognitive processes such as memory and orientation. There exist various culturally adapted versions of the MMSE, such as the Korean MMSE-2 (K-MMSE-2) cases [9]. The Montreal Cognitive Assessment (MoCA) provides a broad assessment of attention, executive function, and visual-spatial abilities [10]. There are also versions adapted to different populations, such as MoCA-K [11]. To allow for comprehensive cognitive assessment, the Consortium to Establish a Registry for Alzheimer's Disease (CERAD-K) battery has been used, both in research and clinical contexts, to evaluate a range of cognitive functions [12]. In addition, the Seoul Neuropsychological Battery (SNSB-II and SNSB-C), which is a holistic battery of cognitive functions, is utilized for differential diagnosis [13]. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) assesses immediate and delayed memory, among other cognitive functions, making it useful for use in longitudinal research studies [5]. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) assesses immediate and delayed memory among other cognitive functions, and thus it is useful for use in longitudinal research studies [14]. These measures are useful for quantifying cognitive impairment, tracking the progression of disease, and differentiating AD from other dementias. However, elements of clinical judgement in the results and a tendency for reduced specificity for early detection necessitate caution and consideration of diagnostic adjuncts.

2.3. Neuroimaging techniques

The main neuroimaging modalities available to help clinicians investigate and assess AD are Structural MRI and PET, which allow in vivo visualization of the pathological signs and symptoms of the disease. sMRI is particularly utilized to identify in vivo cerebral atrophy - more specifically, the pattern of atrophy showing the hippocampus and the entorhinal cortex to be the first cerebral regions affected by AD-related neurodegeneration. While sMRI quantifies the neurodegeneration within the AT(N) (Amyloid, Tau, Neurodegeneration) framework because all dementia has overlapping patterns to the neurodegeneration process stage—it is not brain and AD-specific [15]. PET imaging is more specific: Amyloid PET will identify amyloid-beta plaques via tracers such as florbetapir and can provide a quantitative measure of amyloid-β, showing high-confidence diagnosis, especially for AD at the early stages [16]. PET imaging is more targeted: Amyloid PET will identify amyloid-beta plaques via tracers such as florbetapir and can provide a quantitative measure of amyloid-β, signifying a high-fidelity diagnosis, especially for early-stage AD. At Tau PET can image neurofibrillary tangles and provide an AD-associated neurodegeneration progression stage [7]. Likewise, 18F-Fluorodeoxyglucose PET (18FDG-PET) can measure glucose metabolism, indicating hypometabolic activity in the temporoparietal and posterior cingulate regions—demonstrating neuronal injury—but its specificity for AD is also limited [17]. As these approaches go a long way to improve the diagnostic accuracy of AD, clinicians must leverage clinical data along with neuroimaging when differentiating AD from other neurodegenerative disorders, like frontotemporal dementia, with which AD-related imaging characteristics are shared [18].

2.4. Biomarker-based diagnostics

Biomarker-based diagnostics play a crucial role in differential diagnosis, early detection, and monitoring AD progression. This information can reveal pathological processes before the onset of clinical symptoms, representing an emerging field in the study of AD. CSF analysis assessing levels of Aβ42, total tau, and phosphorylated tau (p-tau) can indicate AD by showing lower levels of Aβ42 and higher levels of tau/p-tau (which can be seen at various points of the disease continuum, including that of the preclinical stage [15]. New biomarkers in CSF, such as neurogranin and synaptic proteins, contribute additionally to the detection of early synaptic dysfunction, an aspect of AD [19]. Complementing CSF testing, new advances in blood biomarkers have introduced highly sensitive plasma tests for amyloid-beta, phosphorylated tau (e.g., p-tau217), neurofilament light chain (NfL), and glial fibrillary acidic protein (GFAP) with excellent correlations with CSF and PET [16]. Biomarkers in blood offer a less invasive and more accessible diagnostic alternative, making them even more appealing for translation into everyday clinical practice. By detecting early and discriminating between AD and other neurodegenerative conditions, biomarker-based approaches considerably improve the precision of diagnosis and enable effective monitoring of disease [20].

In addition to neuroimaging and biomarker-based tests, other tools can assist in the diagnosis and investigation of AD and provide additional insights into mechanisms. Electroencephalography (EEG) affords useful information about neuronal synchronization and connectivity, with AD-related changes reflecting slowed rhythms; however, it remains somewhat limited clinically versus in research [21]. Genetic testing uncovers risk factors, specifically the APOE ε4 allele, accounting for 60–80% of AD heritability, and rare mutations in APP, PSEN1, and PSEN2 genes, which are linked to familial AD; however, genetic testing is typically only for exceptional circumstances and not for routine practice [7],[22]. Artificial intelligence and machine learning models, like XGBoost, explore multiple datasets, comprising cognitive, imaging, and lifestyle variables, and identify risk for AD while determining feature importance using metrics such as Shapley values for early diagnosis in research contexts [17]. Emerging neurotechnological methods, including optogenetics, transcranial magnetic stimulation, and nanotechnology (e.g. magnetic nanoparticles and quantum dots), are being investigated for diagnostic promise, especially in experimental environments [23]–[25]. These tools, while primarily research-oriented, contribute to the understanding of AD and hold promise for eventual clinical application.

3. Standardized diagnostic frameworks

Systematic diagnostic models were developed to improve the precision and reliability of AD diagnosis by incorporating clinical and biological information, particularly for making early-stage case diagnoses. Historically, the NINCDS-ADRDA Criteria, developed in 1984, defined AD as a clinicopathological disorder, founded upon clinical characteristics of progressive loss of memory, yet the criteria were not without faults due to inconsistent correlations between clinical symptoms and autopsy pathology findings [26]. The National Institute on Aging-Alzheimer's Association (NIA-AA) updates from 2011 and 2018 represented a step toward allowing clinical-biological diagnosis as they incorporated biomarkers, including proteins identified through CSF extraction and PET, to facilitate diagnosis and proposed preclinical AD diagnostic criteria in the establishment of a risk state with a biomarker and without clinical evidence [8],[23],[27]. The 2021 International Working Group (IWG) Criteria for AD Diagnosis advance diagnostic specificity, and use both clinical phenotype in tandem with biomarkers to facilitate specificity for atypical presentations of AD and in a heterogeneous patient population [8]. The frameworks as a whole provide a consistent AD diagnosis that includes clinical evaluation with biological markers to maximize the accuracy of diagnosis, particularly in preclinical and early stages, resulting in improved opportunities for early intervention and research.

4. Blood-based laboratory kits: Mechanisms and examples

By utilizing the detection of molecular biomarkers like tau proteins, including phosphorylated variants like p-tau217 and p-tau181, and amyloid-beta (Aβ42, Aβ40), blood-based laboratory kits offer a revolutionary approach to AD diagnostics that makes diagnosis easier and more accessible. These kits usually use sophisticated methods to analyze plasma or serum samples, like enzyme-linked immunosorbent assay (ELISA) for economical, high-throughput screening or liquid chromatography-mass spectrometry (LC-MS) for accurate protein quantification [19]. The tests work because these analytical methods are very sensitive and specific, which means they can find biomarker profiles that are specific to AD and strongly linked to CSF and PET results. This lets doctors find AD pathology without having to do surgery [8]. The main benefit of blood-based kits is that they are simple and easy to scale. A routine blood draw done in a clinical setting means that lumbar punctures and expensive neuroimaging are not needed, making diagnostics more fair and available to more people [18]. High-sensitivity tests like those made for p-tau217 are examples of tests that have shown promise in telling AD apart from other neurodegenerative diseases [28]. Blood-based laboratory kits advance spontaneous detection and tracking of AD non-invasively and practically into clinical practice.

4.1. Commercial offerings

The AD-Detect™ Test, launched by Quest Diagnostics in 2023, represents a major advancement in blood-based biomarker assays for AD, facilitating non-invasive screening for early diagnosis. Priced at $399 and sold direct-to-consumer, the test assesses the amyloid-beta 42/40 (Aβ42/Aβ40) ratio in plasma, a biomarker of amyloid plaque buildup in the brain, using a blood draw performed at Quest Diagnostics collection sites and analyzed in certified laboratories [29]. At 90% accuracy in symptomatic adult populations, the AD-Detect™ Test is developed to be used as a preventive screening test for those with concerns about cognitive health, or for practitioners who want to identify risk for AD in their patients [35]. The Food and Drug Administration (FDA) has not yet approved the test, and its role as a diagnostic instrument awaits validation and incorporation into formal clinical protocols [30]. Despite the AD-Detect™ Test enhancing access to AD screening using a consumer model, its dependence on the Aβ42/Aβ40 ratio highlights that additional biomarkers, such as phosphorylated tau, and clinical correlation should be considered to establish diagnostic specificity and dependability in different populations [31].

4.2 Research innovations

Research in blood-based biomarkers for AD has progressed the field into earlier and more accurate preclinical detection that is also less invasive than current gold standards. A comprehensive study out of Washington University found that plasma p-tau217 reached diagnostic accuracy comparable to CSF testing and sensitivity and specificity nearly equal to lumbar punctures with CSF sampling. Just as promising is plasma p-tau181, which has demonstrated the ability to predict changes in AD brain state using plasma samples up to eight years prior to clinical symptoms of the disease. Early diagnosis offers the opportunity to implement effective intervention strategies. However, while promising, blood-based biomarkers remain in clinical research. Blood-based biomarkers of AD need more validation research and require standardization before practical clinical application [32]. New approaches are also being introduced to enhance sensitivity and specificity for the diagnosis of AD, including a study in 2019 that developed tags on fluorescent nanoparticles to measure microRNAs and amyloid-beta and tau proteins, by enhancing the biomarker signal resonance, both of which increased the likelihood of detecting AD pathology and disease [33]. Additionally, the Hong Kong Center for Neurodegenerative Diseases (HKCeND) is actively developing a blood-based diagnostic kit focused on protein markers [34]. These advances highlight the changing nature of blood-based diagnostics for AD that have enormous potential for transformational change, but also present new challenges to bring research findings to reality as affordable and scalable clinical solutions.

4.3 The case for early detection

It is essential to recognize the pressing need for early diagnosis of AD based on the urgency of time to maximize therapy and practical benefits. The FDA has now approved disease-modifying therapies, which include lecanemab and donanemab, both of which make way for AD treatments that focus on amyloid plaque, which in clinical trials shows optimal efficacy during the mild cognitive impairment (MCI) or early dementia stage of disease before axonal and neuronal loss, and irreversible brain damage [35],[36]. If the diagnosis is delayed, it is unlikely that a patient would receive treatment during the optimal time period, causing a large loss of the opportunity for treatment. In addition to pharmaceutical treatment options, early diagnosis also allows for making lifestyle changes such as dietary improvements, more physical activity and improved sleep hygiene—all associated with a deceleration of disease progression [37]. Early diagnosis also allows families to consider future care needs and determine their financial needs for care, which tends to reduce the emotional burden and logistics of day-to-day concerns. On an additional note, early diagnosis will also allow enrollment opportunities in clinical trials, which support the rapid progression of new therapies as well [3]. To quote the Alzheimer's Association, "Early diagnosis is about empowerment." Blood-based biomarker testing will allow patients to not only access an early diagnosis (as outlined in Alt and Garrido), but it may also catalyze transformation in early detection across the health care continuum and into actual practice — therefore embedding early detection as a regular occurrence in Alzheimer's care.

5. Limitations and controversies

While blood-based biomarker testing for AD could represent a game-changing advancement, some major barriers and issues must be addressed to have a viable and effective clinical application. For example, the AD-Detect™ Test has garnered debate and discussion, particularly because of its lack of FDA approval and notable old-age-specific modest specificity, allowing for potential false positives, causing undue stress and excess demand for subsequent evaluations [38]. Understandably, physicians are reluctant to apply these tests in practice since there are currently no clinical guidelines about how to process and act on probabilistic "risk" results. The outputs from these tests do not provide a definitive diagnosis; they provide a score that will necessitate confirmatory studies for patients, such as PET scans or large batteries of cognitive testing [39]. Technical limitations make them less useful as biomarker levels (e.g., amyloid-beta and phosphorylated tau) can be influenced by age, genetic background, comorbidities, etc., leading to lower diagnostic utility [40]. Moreover, the financial challenges of blood tests like AD-Detect™, which has a retail price of $399, not including laboratory fees, represent a major barrier to access, especially in low-resource contexts [41]. Furthermore, access to advanced assays such as p-tau217 is limited to research sites currently, further restricting use in a clinical setting [42]. Overall, there are considerable barriers regarding the refinement, standardization, and equitable use of blood-based AD diagnostics.

6. Comparative analysis of blood tests

A comparative analysis of blood-based biomarker tests for Alzheimer's disease (AD) highlights a spectrum of advantages and limitations, reflecting trade-offs among accessibility, accuracy, and clinical utility (Table 1).

Table 1. B-based biomarker tests for Alzheimer's disease.

Test Name	Biomarker Measured	Availability	Accuracy	Notes	References
AD-Detect™ (Quest)	Amyloid-beta 42/40 ratio	Direct-to-consumer	~90% (claimed, symptomatic adults)	Not yet approved by the FDA; identifies risk but not diagnostic concern relates to specificity and false positives.	[43]
p-tau217 Test	Phosphorylated tau 217	Research/clinical	Comparable to CSF (~95% sensitivity)	Not yet approved by the FDA; identifies risk but not diagnostic concern relates to specificity and false positives.	[44]
Plasma p tau181 Test	Phosphorylated tau 181	Research/clinical	~90% (preclinical and symptomatic)	Detects AD pathology 8+ years from symptoms. Further validation in diverse groups is required.	[45]

AD, Alzheimer's disease; CSF, cerebrospinal fluid; FDA, Food and Drug Administration

This suggests a full continuum: AD-Detect™ focuses on access, while the p-tau tests focus on accuracy. All of these could still be modified to enhance the sensitivity (correctly identifying true cases) versus specificity (correctly rejecting false positive cases) continuum.

7. Ethical and practical considerations

The identification of AD and the desire for early detection raise grave ethical and practical issues. The experience of a positive biomarker assessment in asymptomatic individuals, particularly in the absence of a successful treatment, can create significant emotional distress as the patient grapples with an uncertain future and limited therapeutic options [46]. This leads to an important question: Is it ethical to screen asymptomatic patients? The Alzheimer's Association sounded a note of caution and has recommended the validation of biomarkers across ethnicity and age to ensure fairness and equity [47]. By forgoing this validation, screening holds the potential for misdiagnosis or bestowing disproportionate benefits to certain populations, which may further exacerbate existing disparities in health.

From a practical perspective, cost and access remain significant obstacles. Tests like AD-Detect™ are now priced at $399, making them unaffordable for many and amplifying health inequities [48]. Insurance coverage of the tests is typically limited or nonexistent, further restricting access to this needed test, with low-income individuals bearing the brunt of access restrictions. Finally, follow-up and failed assessment diagnostic tools, including PET_scans and specialized cognitive assessments, may not be available in rural communities, amplifying health access needs and health disparities in AD care. Altogether, these issues highlight the importance and necessity for policies addressing affordability, access, and equitable implementation of early detection tools, so that all populations benefit from advances in AD and further the goal of equity in AD diagnostics.

8. Future directions: Advancing alzheimer's diagnosis with blood tests

The future of blood-based biomarker tests in AD seems bright, but progress will be slow. At the 2024 Alzheimer's Association International Conference, new blood tests showed potential to greatly reduce diagnostic delays and improve the efficiency of clinical trials [49]. The tests measure biomarkers such as plasma p-tau181 and Aβ42/40 ratio, both of which have excellent sensitivity and specificity for differentiating AD pathology [50]. Experts cite that it will take anywhere from 5-10 years before these tests are widely available, pending large-scale validation studies, regulatory approvals (e.g., FDA clearance), and a drop in costs [51].

Technological advancements, such as the use of artificial intelligence (AI) for data analysis or the creation of multi-biomarker panels, could potentially increase the applicability and predictability of these tests [52]. AI-powered algorithms can help decipher complex biomarker data to address the community bias that exists in the identification of complex biomarker data by enabling standalone tests with greater accuracy in differentiating AD and other dementias [35]. Innovative developments could position blood-based biomarker kits as a new standard of care for AD, ultimately working to improve early diagnosis, tailored treatment approaches, and quality of care. However, this goal will need to address the existing challenges with how these advancements will be accessible, affordable, and equitable. The inequity in healthcare, especially among rural or those with limited access to healthcare systems, must be addressed so these transformative tools can reach all people at-risk of or living with AD.

9. Conclusion

Testing for blood-based biomarkers—like the AD-Detect™ Test for the more recently established p-tau217 tests— has driven a titanic revolution in AD detection. Compared to CSF sampling and neuroimaging, they provide a simple, inexpensive, and relatively non-invasive approach. Amyloid-beta and tau (signature markers of AD pathology) have become more specific tests. But there are challenges:test accuracy variability in mixed populations, the ethics of early diagnosis and attendant psychological distress for asymptomatic individuals, market-level access, and cost issues.

The development of disease-modifying treatments, including lecanemab, highlights the importance of early identification of AD and, therefore, therapeutic decisions made and the retardation of the disease. If blood-based quantifiers can be properly validated, diagnosed, and integrated into the clinician's practice, there may be a vision of AD no longer being an end-stage, devastating illness, but one that can be identified and treated much earlier. Though promising, this promise can only be realized with continued research toward enhancing standardization of assays, further government-driven policy development addressing issues of access and cost, and an unshakable commitment to equity, ensuring these advances benefit all at risk for or affected by AD. The future of AD treatment hangs in the balance of whether science and society can meet these challenges.

10. Author contribution statement

Ahmet ALBAYRAK conceptualized and designed the study, provided a critical review of the manuscript, and oversaw the entire research process.

11. Ethics committee approval and conflict of interest statement

There is no need for ethics committee approval, and there is no conflict of interest for this paper.

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