Improving Early Diagnosis of Amyotrophic Lateral Sclerosis: A Multimodal Literature Review

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Abstract *— Amyotrophic lateral sclerosis (ALS) is a rare, progressive neurodegenerative disorder characterized by the degeneration of upper and lower motor neurons. Due to the clinical heterogeneity of the disease, early diagnosis remains a critical challenge. This study presents a systematic literature review aimed at identifying diagnostic methods that facilitate early ALS detection. Relevant peer-reviewed studies published between 2020 and 2026 were analyzed using a thematic approach, focusing on clinical evaluation, neuroimaging, electrophysiological techniques, biomarker-based methods, and emerging artificial intelligence applications. Findings indicate that while electromyography and neuroimaging are currently the most widely used diagnostic methods, the integration of biomarker research and AI-assisted decision-making holds promise for improving early detection. The review highlights existing gaps in diagnostic sensitivity and accessibility, emphasizing the need for multimodal approaches to reduce diagnostic delays. These insights aim to guide clinicians, researchers, and healthcare professionals in implementing strategies that improve early identification of ALS and patient outcomes.*

Keywords *— Amyotrophic Lateral Sclerosis, Diagnosis, Neurodegenerative Disorder, Neuroimaging.*

PROBLEM STATEMENT

This work consists of a documentary investigation based exclusively on the review and synthesis of previously published scientific literature. All information used in this research is obtained from peer-reviewed scientific articles, clinical reports, and academic studies. No experimental trials, clinical interventions, or direct patient data analyses are conducted. Any patient information referenced in this study is extracted exclusively from previously published scientific sources. This approach allows integrating existing evidence to provide a broader understanding of the research problem and potential diagnostic solutions.

The importance of this research lies in the urgent need to improve the early detection and diagnosis of amyotrophic lateral sclerosis (ALS), a rare, progressive, and currently incurable neurodegenerative disease. ALS primarily affects motor neurons responsible for voluntary muscle control, gradually leading to muscle weakness, paralysis, and respiratory failure. Current treatments only partially slow the progression of the disease, leaving patients with progressive disability and limited life expectancy. Improving early diagnosis could provide significant benefits in clinical management, treatment planning, and patient quality of life.

The motivation for this work stems from a real clinical case in which the initial symptoms of ALS were misinterpreted due to their apparent simplicity. A patient initially experienced mild weakness in one leg, which was initially attributed to minor muscular or neurological issues. Over time, the symptoms dependence on assistive devices, and eventually the loss of mobility. The patient was ultimately diagnosed with ALS at an advanced stage of the disease. Earlier detection could have enabled earlier clinical intervention and improved disease management. This case highlights the need for more reliable and accessible diagnostic methods that can identify ALS at its early stages.

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Investigation Description

This research focuses on identifying, through systematic review and synthesis of published scientific evidence, diagnostic methods, biomarkers, and clinical assessment methods that can contribute to the early detection of amyotrophic lateral sclerosis. The study evaluates the diagnostic performance, clinical applicability, and feasibility of these methods in healthcare and research settings.

ALS is frequently diagnosed only after significant neurological damage has already occurred, primarily because early symptoms often resemble those of other neuromuscular disorders. As a result, diagnosis is commonly delayed. Early detection could significantly improve patient management, facilitate earlier access to therapeutic interventions, and enable patients to participate in clinical trials aimed at developing new treatments.

Objectives of the Investigation

The main objective of this research is to identify evidence-based diagnostic methods and clinical criteria that facilitate the early diagnosis of amyotrophic lateral sclerosis.

Specific objectives include:

- To review existing diagnostic frameworks used in ALS identification.
- To analyze current diagnostic methods, such as neuroimaging and electrophysiological methods.
- To examine the role of biomarkers in ALS detection.
- To explore emerging technologies, including artificial intelligence, that may support earlier diagnosis

Contributions of the Investigation

The primary contribution of this research is a comprehensive review of current diagnostic methods and approaches for early detection of ALS. By synthesizing existing scientific evidence, this study aims to provide a clear, up-to-date overview of diagnostic strategies that may support improved clinical decision-making.

Early identification of ALS may allow healthcare professionals to initiate therapeutic interventions sooner, potentially slowing disease progression and improving quality of life. Currently, the average survival time after diagnosis ranges from 2 to 5 years, underscoring the importance of early diagnosis in patient care.

Overview of ALS

Amyotrophic lateral sclerosis (ALS) is a progressive degenerative disorder that targets the nervous system. By damaging motor neurons, ALS weakens muscles, initially leading to muscular atrophy and progressively paralysis, as shown in Figure 1. In late stages, the patient's respiratory system begins to shut down, ultimately leading to the patient's death at an average of two to five years after being diagnosed.

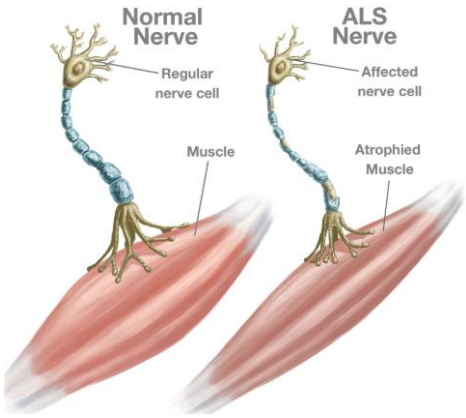

Figure 1

Normal Muscle vs. ALS-affected Muscle Comparison [1]

Despite technological advances, the diagnosis of ALS is highly complicated, as there is no current specific test that certainly determines if symptoms are linked to the disease. Diagnosis is primarily based on clinical evaluation that excludes other neurological disorders, often leading to delayed identification in the early stages of the disease. Similar to treatments, ALS doesn't have a cure, with current drugs only slowing the progression of the disease. Table 1 includes detailed definitions of

key concepts used in this review, derived from, but not limited to, established clinical sources [2, 3].

Table 1
Key Terms and Definitions

Term	Definition
Amyotrophic Lateral Sclerosis (ALS)	A progressive neurodegenerative disease characterized by the degeneration of upper and lower motor neurons, leading to muscle weakness, paralysis, and eventual respiratory failure.
Motor Neurons	Specialized nerve cells responsible for transmitting signals from the brain and spinal cord to muscles, allowing voluntary movement.
Upper Motor Neurons (UMN)	Neurons located in the motor cortex of the brain that transmit signals to lower motor neurons in the spinal cord
Lower Motor Neuron (LMN)	Neurons located in the brainstem and spinal cord directly control muscle contraction.
Biomarkers	Biological indicators measurable in biological samples, such as blood or cerebrospinal fluid, that may help identify or monitor disease processes.
Electromyography (EMG)	A diagnostic technique used to measure electrical activity in muscles.
Magnetic Resonance Imaging (MRI)	Medical imaging technique used to visualize internal body structures.
Artificial Intelligence (AI)	Computational systems capable of analyzing large datasets and identifying complex patterns that may assist clinicians in diagnostic decision-making.
El Escorial Criteria	A set of internationally recognized clinical guidelines used to diagnose ALS by evaluating the presence of upper and lower motor neuron degeneration across multiple anatomical regions.
Awaji Criteria	A refinement of the El Escorial diagnostic criteria that integrates electromyography findings more directly to improve the sensitivity of ALS diagnosis.

Historical Background of ALS

The medical understanding of amyotrophic lateral sclerosis has evolved significantly since the disease was first discovered in the nineteenth century by the French neurologist Jean-Martin Charcot [4]. This scientist identified ALS as a distinct neurodegenerative condition characterized by the progressive degeneration of both upper and lower motor neurons. At the Salpêtrière Hospital, Charcot transformed what had been a poorhouse for women into Europe's foremost neurology center. He was the first to describe multiple sclerosis as a distinct disease (1868) and later identified amyotrophic lateral sclerosis (ALS) and key features of Parkinson's disease. His classification of neurological disorders and introduction of systematic patient observation reshaped clinical medicine.

Figure 2
Jean-Martin Charcot (1825–1893) [5]

Molecular and Genetic Mechanism of ALS

The ALS molecular mechanism involves a complex of genetic mutations: mitochondrial dysfunction, oxidative stress, protein misfolding, excitotoxicity, and neuroinflammation. These mutations disrupt nerve signals to skeletal muscles, leading to muscular atrophy and paralysis. The diversity of molecular mechanisms involved in ALS contributes to significant variability in clinical presentation, complicating the identification of consistent diagnostic markers across patient populations. Additionally, different combinations of mutations result in distinct symptoms, which divide ALS into distinct classifications. Classification by onset includes three primary forms of ALS: limb-onset, bulbar-onset, and

respiratory-onset [6]. Clinical presentation denotes: classic ALS, primary lateral sclerosis, progressive muscular atrophy, proximal ALS, oculomotor ALS, and spli-hand syndrome [7]. Genetic mutations are another classification of ALS, including C9orf72, SOD1-related, FUS-related, TARDBP-related, and ALS2-related [7].

Clinical Presentation and Classification

Amyotrophic lateral sclerosis shares many clinical features with other neuromuscular and neurodegenerative disorders, including muscle weakness, fasciculations, and fatigue. This clinical heterogeneity complicates early diagnosis and often leads to misdiagnosis during the initial stages of the disease [3]. As a result, ALS diagnosis is primarily based on clinical assessment and the exclusion of other conditions rather than on a definitive diagnostic test. Previous studies have reported a mean diagnostic delay ranging from 9 to 24 months from the onset of initial symptoms to confirmed ALS diagnosis [6]. Early diagnosis is therefore critical for timely access to available disease-modifying therapies, eligibility for clinical trials, early involvement of interdisciplinary care teams, and informed planning for disease management and quality of life.

Diagnostic Challenges

This wide range of clinical and genetic classifications highlights the heterogeneity of ALS, which represents a major barrier to early diagnosis. Differences in symptom onset, progression patterns, and affected motor neuron populations often lead to misdiagnosis or delayed diagnosis, reinforcing the need to evaluate and improve current diagnostic strategies. In addition to researches who's main focus is ALS, studies conducted in other neurodegenerative conditions have explored diagnostic strategies aimed at improving early disease detection and diagnosis. Figure 3 demonstrates the current timeline for ALS diagnosis based on the available diagnostic methods.

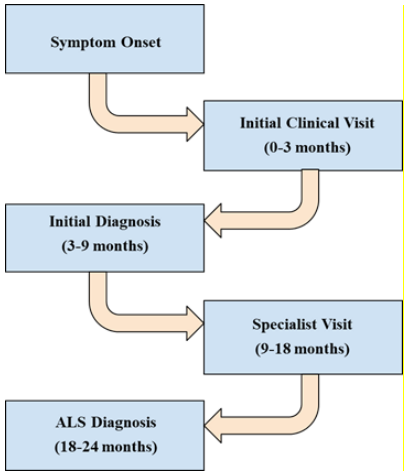

Figure 3
ALS Diagnostic Delay Timeline

Advances in diagnostic frameworks, biomarker identification, and multimodal assessment approaches in related disorders provide valuable insights into how earlier and more reliable diagnoses can be achieved. Studies focused on the use of CSF biomarkers related to neuroinflammation and neurodegeneration, indicating potential biological effects that support the development of ALS therapies [8]. Examining these studies offers a broader perspective on the current diagnostic landscape and outlines potential pathways to improve early diagnosis in ALS. Table 2 summarizes common diagnostic challenges in ALS.

Table 2
Diagnostic Challenges in ALS

Challenge	Description	Impact on Diagnostic
Diagnostic Delay	The time between symptom onset and confirmed diagnosis ranges from 9 to 24 months	Delays treatment initiation and reduces opportunities for early intervention
Lack of Biomarkers	No validated biological marker exists to definitively confirm ALS	Diagnosis relies on exclusion, increasing uncertainty, and variability
Clinical Heterogeneity	Variability in symptom onset, progression, and affected motor neurons	Makes early-stage recognition difficult and leads to inconsistent clinical interpretation

Symptom Overlap	ALS symptoms resemble other neuromuscular and neurodegenerative disorders	Increases risk of misdiagnosis and inappropriate treatment
Limited Access to Tools	Advanced diagnostics (EMG, MRI) require specialized equipment and expertise	Restricts early diagnosis in resource-limited settings
Reliance on Clinical Judgment	Diagnosis heavily depends on the physician's expertise	Introduces subjectivity and variability across healthcare providers

Diagnostic Frameworks

One of the most widely used diagnostic frameworks for ALS is the "El Escorial Criteria", developed to standardize ALS diagnosis in both clinical practice and research [9]. These criteria classify ALS based on the presence of upper and lower motor neuron degeneration in multiple anatomical regions. Later refinements, including the Revised El Escorial Criteria and the Awaji Criteria, were introduced to improve diagnostic sensitivity, particularly during the early stages of the disease. The Awaji criteria, for instance, integrate electrophysiological findings obtained through Electromyography with clinical observations to enhance early detection. Although these frameworks have improved diagnostic consistency, their effectiveness still depends heavily on clinical expertise and access to specialized neurological evaluation.

Current Diagnostic Methods

Because ALS lacks a definitive diagnostic biomarker, physicians rely on a combination of clinical evaluation and complementary diagnostic tests. Among the most commonly used tools is Electromyography, which helps detect abnormalities in muscle electrical activity associated with motor neuron degeneration. In addition, neuroimaging techniques such as Magnetic Resonance Imaging (MRI) are frequently used to exclude other neurological conditions that may mimic ALS symptoms. Laboratory studies, including Cerebrospinal Fluid Analysis, may also help rule out inflammatory or infectious neurological disorders. Although these diagnostic methods provide valuable clinical information, none alone can definitively confirm ALS, underscoring the need for improved diagnostic strategies and the identification of reliable biomarkers.

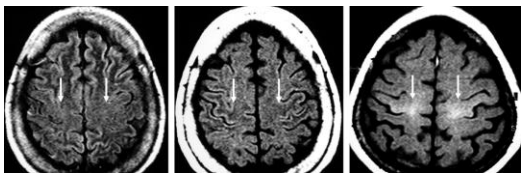

Figure 4
MRI Scan Comparison of a Healthy Brain (Left and Middle) vs an ALS-affected Brain (Right) [10]

Emerging Diagnostic Approaches

In addition to these studies, researchers have begun using artificial intelligence (AI) to support more effective and accurate diagnosis, particularly in complex neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS). The majority of clinical decision-making continues to rely primarily on human reasoning. This approach has been foundational in medical practice, but it still represents a single perspective, limiting the range of diagnostic possibilities to be considered. To address this gap, recent work has introduced artificial intelligence–supported shared decision-making (AI-SDM) [11]. This conceptual framework integrates predictive modeling, evidence synthesis, and generative AI into the clinical decision-making workflow. AI-SDM doesn't serve as a substitute for conventional clinical decision-making; rather, it positions AI-SDM functions as a reasoning facilitator. By providing transparent, human-interpretable justifications, symptoms can be evaluated and discussed by healthcare professionals and patients, enhancing decision quality, supporting evidence-based practice, and preserving patient autonomy.

Comparative Discussion and Challenges

Despite improvements in clinical criteria and diagnostic technologies, several challenges continue to limit the early detection of ALS. The

disease exhibits significant clinical heterogeneity, meaning that symptom onset, progression patterns, and affected motor neuron populations can vary widely among patients. Additionally, many early symptoms of ALS overlap with those of other neuromuscular disorders, often leading to misdiagnosis or delayed diagnosis. Another major limitation is the lack of validated biological biomarkers to confirm the disease at its earliest stages. As a result, ALS diagnosis often occurs only after substantial neuronal damage has already taken place. These limitations highlight the importance of continued research to develop more sensitive diagnostic methods, including biomarker-based approaches and emerging technologies such as artificial intelligence–assisted diagnostic systems.

Given the complexity and heterogeneity of ALS, a wide range of studies have explored various diagnostic approaches, biomarkers, and clinical assessment strategies to improve early detection. The existing literature can be broadly grouped into diagnostic methodologies, study objectives, and technological approaches, reflecting both historical and recent efforts to address the limitations of current diagnostic practices. Reviewing and synthesizing these studies is essential to identify strengths, limitations, and gaps that inform potential improvements in ALS diagnosis and treatment.

METHODOLOGY

This research will be conducted using a qualitative descriptive methodology based on a literature review. This study aims to analyze and synthesize existing scientific evidence related to the early identification of amyotrophic lateral sclerosis (ALS) and the diagnostic methods currently available. Relevant information will be selected through a structured and systematic search of peer-reviewed publications.

Information for this literature review will be collected from multiple academic databases, including Springer Nature Link and institutional library resources. The search strategy will include keywords such as “amyotrophic lateral sclerosis,” “early diagnosis,” “electrodiagnostic,” “neuroimaging,” “biomarkers,” and “artificial intelligence,” used both individually and in combination. To ensure comprehensive coverage, the review will include peer-reviewed articles published between 2020 and 2026.

Once the relevant literature is selected, the information will be organized and analyzed using a thematic analysis approach. Diagnostic methods will be grouped into the following defined categories: neuroimaging, electrophysiological, biomarker, and artificial intelligence. Some studies may include multiple categories, which will be analyzed based on their primary contribution to ALS diagnosis.

Within each category, the literature will be examined to compare reported accuracy, effectiveness, and accessibility. Rather than relying solely on quantitative measures, this analysis will emphasize qualitative comparisons across studies to identify consistent patterns, strengths, and gaps in current diagnostic approaches. This analytical framework will facilitate the identification of key diagnostic challenges and highlight opportunities to improve early detection of ALS through a more integrated, multimodal diagnostic strategy.

The research methodology for this review will follow the following sequential process:

- Using selected academic databases and predefined keywords, a comprehensive literature search will be conducted.
- Retrieved articles will be screened based on inclusion and exclusion criteria to ensure relevance and quality.
- Relevant data will be extracted and organized by diagnostic category.
- Collected information will be analyzed using a thematic approach.
- Findings will be synthesized and discussed.

RESULTS AND DISCUSSION

As shown in Table 3, this analysis follows the same structure defined in the methodology, in

which diagnostic approaches for amyotrophic lateral sclerosis (ALS) were categorized into clinical evaluations: neuroimaging, electrophysiological techniques, biomarker-based methods, and artificial intelligence. Through a systematic review of selected literature, each diagnostic method was analyzed for effectiveness, accuracy, accessibility, and limitations.

Table 3
Filters for Selected Literature

Filters	Article 1	Article 2	Article 3
DataBase	Springer Nature Link	Springer Nature Link	Springer Nature Link
Keywords	ALS Misdiagnosis	Artificial Intelligence in ALS Diagnosis	Artificial Intelligence in ALS Diagnosis
Content Type	Article	Article	Article
Publishing Model	Open Access	Open Access	Open Access
Date Published	2020-2026	2020-2026	2020-2026
Languages	English	English	English
Subjects	Amyotrophic Lateral Sclerosis	Amyotrophic Lateral Sclerosis	Amyotrophic Lateral Sclerosis
Discipline	Medicine and Public Health	Medicine and Public Health	Medicine and Public Health

Analysis of Article #1

The article "Brain Metabollic Differences between pure bulbar and pure spinal ALS" [12] discloses the metabolic features that characterize ALS patients with spinal motor impairment by evaluating 2-[18F]FDG-PET brain capabilities. For the purpose of this investigation, the article emphasizes both neuroimaging and electrophysiological aspects. Biomarkers are partially mentioned, while artificial intelligence (AI) is not addressed.

Electrophysiological techniques are emphasized as one of the most critical tools for ALS diagnosis. EMG is highly effective in detecting abnormalities in muscle electrical activity that reflect underlying motor neuron degeneration, such as the Awaji algorithm. Accessibility is somewhat limited, as EMG requires specialized equipment and trained professionals, which may not be available in all healthcare settings. Overall, the article talks highly about electrophysiological techniques, supporting its high accuracy and effectiveness rating.

The article presents neuroimaging, particularly MRI, as a supportive diagnostic tool in ALS rather than a definitive method. Its primary purpose is not to diagnose ALS but to identify other neurological conditions that may mimic ALS symptoms. In terms of accessibility, MRI is widely available in many clinical settings, though access may vary depending on healthcare infrastructure. While it can reveal structural and functional abnormalities associated with motor neuron degeneration, these findings are not specific enough to confirm ALS on their own; hence, it is rated lower than electrophysiological techniques in this article.

Biomarkers are mentioned in the article but are not a central focus of the discussion, reflecting their current status as emerging rather than established diagnostic methods in ALS. The article suggests that while biomarkers hold promise for improving early detection and understanding disease progression, their clinical application remains limited due to insufficient validation and standardization.

The article does not address artificial intelligence, suggesting it does not contribute to the diagnostic framework discussed by the authors. This absence highlights a gap between traditional diagnostic approaches and emerging technologies, reinforcing the need for future research integrating AI into ALS diagnosis to enhance accuracy and reduce diagnostic delays.

Analysis of Article #2

The article "Update on recent advances in amyotrophic lateral sclerosis" [13] summarizes scientific highlights in ALS research published over the last 60 months. It highlights the complexity of ALS as a heterogeneous neurodegenerative disorder and underscores the limitations of traditional diagnostic approaches that rely heavily on clinical evaluation and exclusion of other conditions. To address these challenges, the study explores the

growing role of complementary diagnostic methods, including advanced neuroimaging techniques, biomarker-based approaches, and electrophysiological tools. In addition, it briefly considers emerging technologies, such as artificial intelligence, as potential future contributors to diagnostic innovation.

Neuroimaging is one of the article's strongest components, explaining how this technique can detect corticospinal tract degeneration, cortical thinning, and extramotor involvement, even in early or presymptomatic stages. It also discusses prognostic applications and patient stratification using imaging biomarkers. This level of detail and clinical relevance justifies the highest score.

Electrophysiological methods are mentioned primarily in the context of diagnostic criteria, particularly within the Awaji criteria, where fasciculations are considered evidence of lower motor neuron involvement. It also references tools such as motor-evoked potentials for detecting subclinical upper motor neuron damage. However, there is no deep methodological discussion of EMG or electrophysiology as standalone diagnostic methods, so the contribution remains moderate.

The article provides a comprehensive, highly relevant discussion of biomarkers, highlighting the lack of reliable biomarkers as a major limitation in ALS diagnosis. It highlights key candidates, including neurofilament light chain (NfL), phosphorylated neurofilament heavy chain (pNFH), and inflammatory CSF markers (e.g., CHIT1, YKL-40). It also discusses their roles in diagnosis, prognosis, and treatment monitoring, resulting in a high evaluation score.

The article touches on emerging technologies, including assistive digital tools and wearable monitoring systems, but does not directly address artificial intelligence for ALS diagnosis. While it acknowledges technological innovation in patient care and monitoring, it lacks discussion of AI-driven diagnostic models and machine learning. Therefore, its relevance to this category is limited.

Analysis of Article #3

The article “Predicting functional impairment trajectories in amyotrophic lateral sclerosis: a probabilistic, multifunctional model of disease progression” [14] proposes using an artificial intelligence model to predict and simulate ALS progression. The model would be capable of accounting for via variable interactions, functional impairments, and survival. The article strongly emphasizes both neuroimaging and electrophysiological aspects, while partially mentioning biomarkers, but not artificial intelligence (AI).

In this article, electrophysiological methods are strongly emphasized as a core diagnostic tool for ALS. EMG is essential for detecting lower motor neuron degeneration and plays a central role in diagnostic criteria such as the Awaji and El Escorial frameworks. The article highlights its reliability and clinical importance, making it one of the most effective tools available. Similar to article 1, this article emphasizes electrophysiological techniques, which support its high accuracy and effectiveness rating.

Similar to article 1, this article discusses the use of neuroimaging techniques as a supportive and exclusionary diagnostic tool for ALS. Neuroimaging is useful for ruling out other neurological conditions that may mimic ALS symptoms, such as other types of sclerosis, limiting the ALS-exclusive diagnosis. Accessibility depends mostly on the patient's healthcare providers, which can sometimes limit MRI availability, making neuroimaging a moderate evaluation method.

Biomarker research is mentioned but not deeply explored in the article. When mentioned, it is discussed as reflecting the current limitation in ALS diagnostics, where no validated biomarker exists for definitive diagnosis. While there is ongoing interest in neurochemical and molecular markers, their clinical application remains limited. As for artificial intelligence, it is not addressed in the article, nor are computational models,

predictive analytics, or AI-assisted decision-making tools.

As seen in Table 4, the analysis of these three articles highlights that the diagnosis of amyotrophic lateral sclerosis remains fundamentally limited by the absence of a single, definitive diagnostic method. This reinforces the need for a complementary, multimodal approach, as the current physical evaluation is limited and serves only as the first point of patient assessment.

Table 4
Evaluation of Diagnosis Methods

Diagnosis Methods	Criteria to be Evaluated	A1	A2	A3
Neuroimaging	Accuracy	2	3	2
	Accesibility	2	2	2
	Effectiveness	2	3	2
Biomarkers	Accuracy	1	3	1
	Accesibility	1	2	1
	Effectiveness	1	3	1
Artificial Intelligence	Accuracy	0	1	0
	Accesibility	0	1	0
	Effectiveness	0	1	0
Electrophysiological	Accuracy	3	2	3
	Accesibility	2	3	2
	Effectiveness	3	2	3

Legend: 0 - Not mentioned; 1 - Limited; 2 - Moderate; 3 - Strong

The analysis of these three articles highlights that the diagnosis of amyotrophic lateral sclerosis remains fundamentally limited by the absence of a single, definitive diagnostic method. This reinforces the need for a complementary, multimodal approach, as the current physical evaluation is limited and serves only as the first point of patient assessment.

Physical evaluation guides the overall diagnostic pathway; however, it is inherently subjective and relies on excluding other neurological conditions or differential diagnosis, which significantly contributes to diagnostic delays. Electrophysiological techniques, particularly electromyography, are among the most reliable tools for detecting lower motor neuron degeneration, yet their reliance on specialized equipment and expertise limits accessibility in some settings. Neuroimaging methods, such as MRI and advanced imaging techniques, provide valuable insight into structural and functional changes and are especially useful for ruling out alternative diagnoses, though the complexity and similarity of ALS to other diseases limit their use as standalone diagnostic methods. Biomarkers represent one of the most promising areas for improving early detection and disease monitoring, but their current lack of validation and standardization restricts their routine clinical use. Finally, although artificial intelligence and computational models demonstrate potential for enhancing prediction and diagnostic precision, their integration into clinical practice remains limited and underdeveloped in the current literature.

Collectively, these findings emphasize that the current evaluation methods possess distinct strengths and weaknesses, and that effective ALS diagnosis depends on their integration rather than on reliance on any single approach. A multimodal approach would take advantage of each method's strengths, allowing to filter out any possible diseases, providing an earlier ALS diagnosis. Clinical evaluation serves as the essential starting point for identifying neurological deficits, with neuroimaging and electrophysiological methods serving as disease filters. Although both remain in early stages of development, biomarkers and artificial intelligence represent emerging areas with the potential to transform future ALS diagnosis. Biomarkers have shown promise for improving early detection and monitoring disease progression; however, their clinical application remains limited by the need for further validation and standardization. In contrast, while recent literature acknowledges the growing interest in artificial intelligence and computational approaches, their direct application to ALS diagnosis remains limited within current studies. As these technologies continue to evolve, they may contribute to a more integrated, data-driven diagnostic framework that complements existing clinical and diagnostic methods.

CONCLUSION

The problem statement of this article stated that the complexity of amyotrophic lateral sclerosis led to delayed diagnosis. This article addresses the statement by presenting a structured literature review demonstrating that current diagnostic practices rely heavily on clinical evaluation and exclusion criteria, resulting in significant diagnostic delays. These findings confirm that no single diagnostic method is sufficient for the early detection of ALS, as represented in Figure 5. Instead, a multimodal approach integrating clinical frameworks (El Escorial and Awaji criteria), electrophysiological techniques (EMG), neuroimaging (MRI), and emerging biomarker-based methods can lead to earlier diagnosis. Biomarkers and artificial intelligence represent promising future solutions; however, both are still in development and lack sufficient validation for routine clinical use. This article confirms that clinical heterogeneity and lack of definitive biomarkers are the main barriers to early ALS diagnosis and supports the problem described in the investigation.

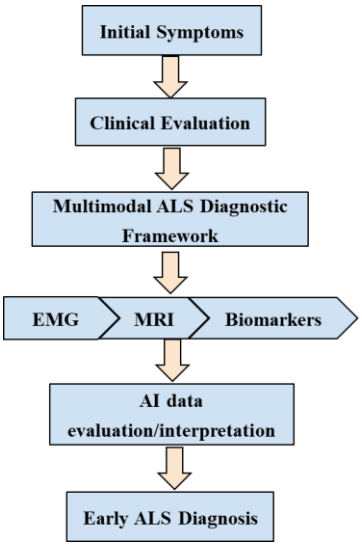

Figure 5
Multimodal ALS Diagnostic Framework

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DISCLOSURE STATEMENT

"*This work used AI tools (Grammarly and ChatGPT) for: brainstorming, research ideas or outlines, grammar, structure, or stylistic editing, and drafting tables, visualizations, or code templates. All interpretations, arguments, and conclusions are the author's own and have been verified for accuracy*".