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

Author: Dail Naded Ruiz Rios
Advisor: Rafael A. Nieves Castro, PharmD.
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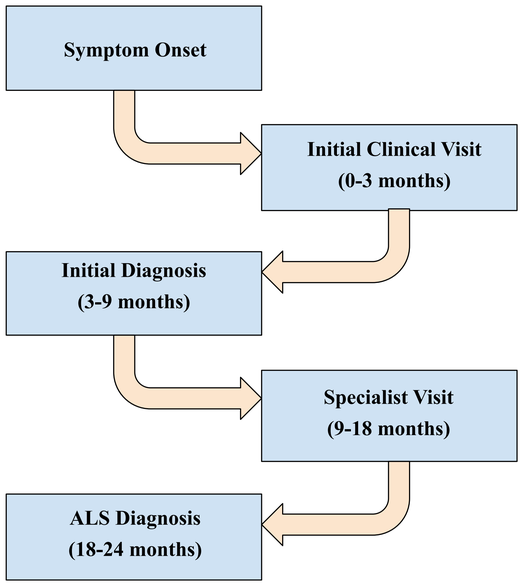
Abstract

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.

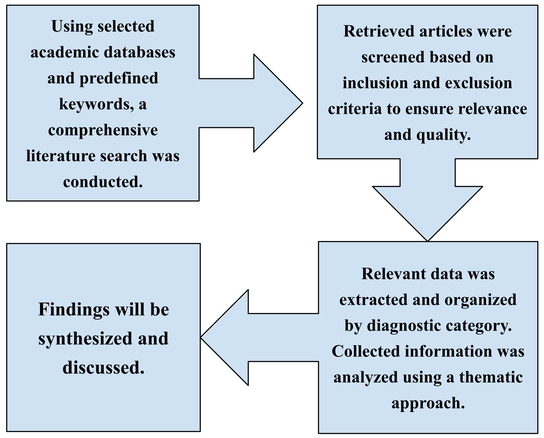
Keywords *— Amyotrophic lateral sclerosis, neuroimaging, diagnosis, neurodegenerative disorder.*

Problem



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.

Methodology



Results and Discussion

After a comprehensive literature search, three (3) articles were screened and a number based score was given and presented on the table below. The evaluation was not made to compare articles on a competitive matter nor total score was taken into consideration for this evaluation. These score demonstrate that ALS diagnosis remains challenging due to the absence of a single definitive diagnostic method. This highlights the importance of a complementary, multimodal approach. Physical evaluation serves as the initial step in patient assessment, but due to the diseases symptom heterogeneity it's excluding criteria often delays diagnosis. Electrophysiological techniques are effective for detecting lower motor neuron degeneration, while Neuroimaging methods are valuable for identifying structural and functional abnormalities and ruling out alternative diagnoses, but they are not sufficient as standalone tools. Biomarkers show strong potential for improving early detection and monitoring disease progression; however, their clinical use remains limited by the need for further validation and standardization. Likewise, artificial intelligence and computational models may improve diagnostic accuracy and prediction, but their application in ALS diagnosis is still in early stages.

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

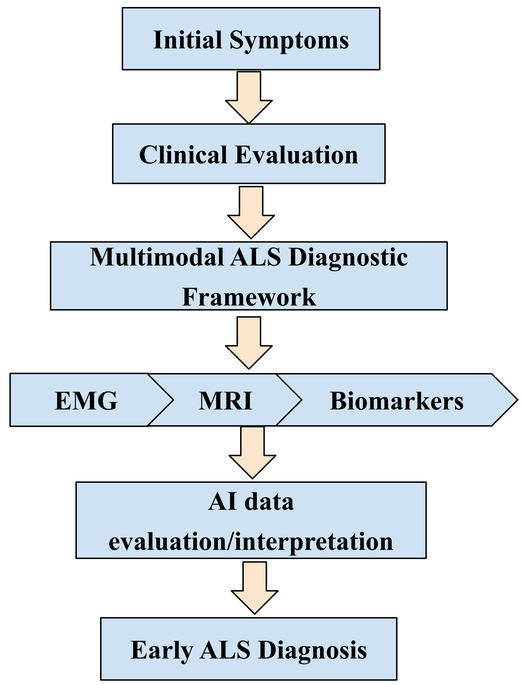
Legend: 0 - Not mentioned 1 - Limited 2 - Moderate 3 - Strong

Results and Discussion (cont.)

Overall, each diagnostic method presents distinct strengths and limitations, reinforcing that effective ALS diagnosis depends on integrating multiple approaches rather than relying on a single technique. Clinical evaluation provides the foundation for identifying neurological deficits, while neuroimaging and electrophysiological studies help exclude other conditions and support diagnosis. As biomarkers and artificial intelligence continue to advance, they may contribute to a more integrated and data-driven diagnostic framework that enhances early detection and improves ALS diagnosis in the future.

Conclusions

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 shown in the figure below, 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.



Future Work

Biomarkers and Artificial intelligence are still in early development. In some years, both tools would most likely serve to aid in the early diagnosis for ALS. If someone where to take the multimodal approach suggested in this literature review, the next step would that of incorporating of both tools into the proposed approach.

Acknowledgements

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I want to extend the gratitudes to myself, for always finding a way to push through. Many people have pushed me forward during this process, but at the end of the day it is us, the students, who know the real sacrifice.

I wish to dedicate this project to all the patients who suffer from ALS but most importantly to their caretakers who, against all odds, sacrifice their wellbeing to care for their loved one. I hope for this work to support the ALS community in finding new ways to fight this disease.

References

[1] K. Painter, "How to Be a Caregiver for Someone With ALS," AARP. [Online] Available: https://www.aarp.org/health/conditions-treatments/amyotrophic-lateral-sclerosis-als/

[2] R. G. Brotman et al., "Amyotrophic lateral sclerosis," StatPearls, National Center for Biotechnology Information, 2024.

[3] National Institute of Neurological Disorders and Stroke, "Motor Neuron Diseases," 2023.

[4] S. A. Goutman et al., "Recent advances in the diagnosis and prognosis of amyotrophic lateral sclerosis," The Lancet Neurology, vol. 21, no. 5, pp. 480–493, 2022, doi: 10.1016/S1474-4422(21)00465-8.

[5] D. R. Kumar, F. Aslinia, S. H. Yale, and J. J. Mazza, "Jean-Martin Charcot: The father of neurology," *Clinical Medicine & Research*, vol. 9, no. 1, pp. 46–49, Mar. 2011, doi: 10.3121/cmr.2009.883.

[6] D. R. Kumar, F. Aslinia, S. H. Yale, and J. J. Mazza, "Jean-Martin Charcot: The father of neurology," Clinical Medicine & Research, vol. 9, no. 1, pp. 46–49, 2011.

[7] R. Raoufinia et al., "Cutting-edge treatments in amyotrophic lateral sclerosis: The role of molecular pathogenesis in targeted therapies," Stem Cell Research & Therapy, vol. 16, no. 1, 2025, doi: 10.1186/s13287-025-04781-w.

[8] P. H. García-Casanova and J. F. Vázquez-Costa, "Advances in the early diagnosis of amyotrophic lateral sclerosis," Expert Review of Neurotherapeutics, vol. 25, no. 4, pp. 415–425, 2025, doi: 10.1080/14737175.2025.2471556.

[9] M. de Carvalho et al., "Awaji diagnostic algorithm increases sensitivity of El Escorial criteria for ALS diagnosis," Amyotrophic Lateral Sclerosis, vol. 9, no. 5, pp. 295–298, 2008.

[10] *Antonio J. da Rocha, et. al. (*2004, October 25). *"American Journal of Neuroradiology" vol. 25* [Online] Available: https://www.ajnr.org/content/25/9/1509/F2.

[11] M. As'ad, N. Faran, and H. Joharji, "AI-Supported Shared Decision-Making (AI-SDM): Conceptual Framework," JMIR AI, vol. 4, p. e75866, 2025, doi: 10.2196/75866.

[12] A. Canosa *et al.*, "Brain metabolic differences between pure bulbar and pure spinal ALS: a 2-[18F] FDG-PET study," *Journal of Neurology*, vol. 270, no. 2, pp. 953–963, 2023, doi: 10.1007/s00415-022-11445-9.

[13] N. Riva *et al.*, "Update on recent advances in amyotrophic lateral sclerosis," *Journal of Neurology*, vol. 271, pp. 4693–4723, 2024, doi: 10.1007/s00415-024-12435-9.

[14] E. Tavazzi *et al.*, "Predicting functional impairment trajectories in amyotrophic lateral sclerosis: A probabilistic, multifactorial model of disease progression," *Journal of Neurology*, vol. 269, no. 7, pp. 3858–3878, 2022, doi: 10.1007/s00415-022-11022-0