**Machine Learning Powered Decision Support System for Early Detection of Amyotrophic Lateral Sclerosis (ALS)**

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**Abstract**

Early diagnosis of Amyotrophic Lateral Sclerosis (ALS) is crucial for patient care and management. This study evaluates the efficacy of machine learning algorithms, particularly a Random Forest classifier, to predict ALS using patient data. Enhancing the data resulted in increased diagnostic accuracy, emphasizing the need for comprehensive datasets in predictive modeling. Initial model accuracy of 62% demonstrates promise but highlights limitations of relying solely on basic clinical data. Remarkable improvement to 97% accuracy with richer data (family history, functional scores, race, genomics) underscores the importance of diverse data sources. Comparative analysis reveals the second model's exceptional precision and recall across all diagnostic categories, suggesting a highly refined and comprehensive approach. These class-specific performances indicate the need for tailored models or feature sets for different ALS phenotypes.

**Introduction**

Amyotrophic Lateral Sclerosis (ALS) presents diagnostic challenges due to its heterogeneity in symptom presentation. Delayed diagnosis impedes timely intervention, making the pursuit of accurate early detection methods imperative. Manifesting symptoms ranging from difficulty walking to muscle weakness, slurred speech, trouble swallowing, and behavioral changes, ALS varies significantly among patients. Notably, it exhibits a male-to-female ratio of approximately 3:1, predominantly affecting individuals between the ages of 55 and 70, as well as some racial variation, as 93 percent of ALS patients ever documented at a healthcare facility were Caucasians. With no known cure, ALS necessitates intensive care, involving a dedicated team of medical professionals, specialized equipment, and comprehensive support for daily living activities. This study explores machine learning's potential in predicting ALS, with an emphasis on diversifying data inputs to improve diagnostic precision (Naqvi, 2019; Crider, 2023).

**Literature Map and Review**

According to the Centers for Disease Control and Prevention (CDC), approximately 30,000 Americans were diagnosed with ALS in 2018, with an average life expectancy of 2 to 5 years post-diagnosis. The economic impact is substantial, with annual costs per patient estimated at $63,693 in 2014, half of which are direct medical expenses (Naqvi, 2019). These figures not only underscore the disease's devastating impact but also highlight the need for more effective diagnostic and therapeutic strategies.

The current landscape of ALS research indicates significant gaps in early diagnosis and management. Studies have explored the application of machine learning in healthcare, including ALS, but the focus has often been on other neurological conditions, leaving a gap in ALS-specific applications. For example, Kocar et al. (2021) provided a comprehensive review of neuroimaging features for diagnosing ALS using machine learning. This review identified key neuroimaging features such as corticospinal tract data, motor cortex metrics, and texture analysis that could be harnessed by machine learning models. While diffusion tensor imaging (DTI) and volumetric data emerged as robust indicators, integrating functional and structural connectivity was highlighted as a complex yet critical area for future research.

Similarly, Fukushima et al. (2022) underscored the potential of Muscle Ultrasonography (MUS) in early ALS detection, particularly its ability to detect fasciculations across various muscles. Their research presented MUS as a non-invasive method that could potentially surpass traditional electromyography in sensitivity. Their development of the MUS-FAST approach, a quick and non-invasive method, showcased comparable performance to other models, indicating a significant leap forward in early ALS detection.

Furthermore, Nathan et al. (2021) explored the use of real-world data from electronic health records to predict early ALS diagnosis. They analyzed data from over 4700 ALS patients, employing machine learning models to identify clinical features indicative of early disease. Their study successfully utilized gradient boosting models, achieving high accuracy in early ALS detection, thus demonstrating the valuable role of machine learning in leveraging healthcare data for ALS diagnosis.

**Objective**

The primary objective of this project is to provide healthcare professionals and patients  
a tool to enable early referral and diagnosis and to provide ALS care providers  
managing ALS at Temple University Hospital ALS hope foundation clinic with a reliable  
tool for diagnostic assessment of ALS. Given the heterogeneity of ALS and the reliance on clinical symptoms for diagnosis, there is a clear need for more precise, early detection methods. This research aims to address these challenges by developing machine learning models capable of accurately predicting ALS disease diagnosis, considering the disease's heterogeneity. This involves the integration of diverse data sources, including clinical records, imaging, and genomics, to create a reliable tool for early clinical decision support for ALS which can aid in ALS clinical management, research, and support. This tool will leverage advanced analytics to provide healthcare professionals with predictive insights tailored to individual patient profiles.

By focusing on these objectives, this project seeks to contribute significantly to the field of ALS, offering potential breakthroughs in early detection and management. The goal is to enhance the quality of life and care for those affected by this challenging disease through innovative, data-driven approaches.

**Research Questions:**

1. How can an ML/AI-powered Decision Support System (DSS) be developed to  
   predict ALS disease progression with high precision, considering the  
   heterogeneity of the disease?
2. How can ML/AI algorithms leverage clinical records, imaging, and genomic  
   information, to improve the early detection of ALS?
3. What ethical considerations, data bias and privacy measures must be addressed when  
   implementing the ML/AI-powered Decision Support System in ALS management  
   and clinical research?

**Methodology**

Data Collection and Preprocessing:

This study utilized a retrospective dataset of 116 patients with ALS or suspected ALS, recruited from the Temple University Hospital ALS clinic. Data were extracted from comprehensive electronic health records, encompassing:

* Clinical characteristics: Demographic information (ID, sex, race), medical history (ALS diagnosis history, age of onset, ALS gene mutations), functional scores (ALSFRS), and risk assessment scores.
* Neurophysiological data: EMG results capturing neuromuscular function parameters.
* Genomic data

The data Entry Criteria for each subject is at least a suspected diagnosis of ALS and one interaction or consultation with a healthcare professional recorded as a separate entry.

Rigorous data cleaning and preprocessing were conducted using Python, including:

* Normalization: Standardizing data to a common scale for consistent analysis.
* Missing value imputation: Employing statistically robust methods like k-nearest neighbors or multiple imputation to address missing data points.
* Outlier detection and handling: Identifying and addressing outliers through robust statistical techniques or manual inspection to avoid biasing model performance.

Feature Engineering and Selection:

To identify the most informative features for ALS diagnosis and prediction, this study employed a multifaceted approach:

1. Clinically relevant data mining: By applying clinical expertise to neurophysiological and genomic data, I identified key features and extracted valuable insights for ALS diagnosis.
2. Statistical feature engineering: Techniques like dimensionality reduction using Principal Component Analysis (PCA) or feature selection methods were implemented to reduce data complexity, mitigate overfitting risks, and identify the most predictive features.
3. Model design and clinical decision support: Building upon the identified features, a Random Forest classifier was designed and optimized in Python. To translate model predictions into actionable recommendations, a three-step system was developed:

* Rule-based system for clinical decision support: This system incorporated evidence-based clinical guidelines and current best practices, providing tailored treatment and management recommendations based on the model's diagnosis. Three protocols were implemented: Standard ALS for definite diagnosis, Probable ALS protocol for probable diagnosis, and conservative symptomatic treatment for possible diagnosis.
* Decision trees: These branching structures further refined the recommendations within each protocol, considering additional patient-specific factors and tailoring treatment plans for optimal patient care.

**Result**

The Random Forest classifier, when applied to the dataset, achieved an accuracy of approximately 62% on the test set with baseline features such as age, sex, and EMG data. Further enhancement of the model with additional variables like Age of onset and ALSFRS score led to a remarkable accuracy leap to 97%.

In the comparative analysis of two Random Forest classifiers trained for the diagnosis of Amyotrophic Lateral Sclerosis (ALS), the performance metrics significantly differed between the two models. The classes under consideration were:

1. Class 1: Definite Diagnosis
2. Class 2: Probable Diagnosis
3. Class 3: Probable Lab-supported Diagnosis
4. Class 4: Suspected Diagnosis
5. Class 5: Possible Diagnosis

For the first classifier, precision scores ranged from 0.50 to 0.75 across the classes, with the highest precision observed in Class 5 (Possible Diagnosis). Recall scores were notably lower, with the lowest at 0.38 for Class 3 (Probable Lab-supported Diagnosis), indicating a substantial number of missed true positive cases. The F1-scores, which balance precision and recall, were consequently moderate, peaking at 0.73 in Class 5 (Possible Diagnosis).

In contrast, the second classifier exhibited precision and recall scores at or near the maximum value of 1.00 for all classes, which was mirrored in the F1-scores. This exceptional performance denotes a classifier that is both highly precise in its predictions and exhaustive in capturing true positive instances across all diagnostic categories.

The discrepancy in performance metrics between the two classifiers is most pronounced in Class 3 (Probable Lab-supported Diagnosis), where the first classifier's recall is only 0.38 compared to 0.99 in the second classifier, reflecting a significant advancement in the model’s capability to identify true positive cases within this category.

**Figure 1**

A screenshot of a computer screen

Description automatically generated

**Figure 2**

**A number of numbers in a row

Description automatically generated with medium confidence**

**Discussion**

This study marks a significant step in leveraging machine learning for early ALS detection. While current diagnostic methods rely on clinical symptoms, often leading to delayed diagnoses and hindering timely intervention, the research aimed to bridge this gap by exploring the potential of data-driven approaches. The study utilized a Random Forest classifier trained on a comprehensive dataset of 116 patients from Temple University Hospital's ALS clinic. This data encompassed a rich tapestry of clinical records, risk assessments, EMG results, and genomic information, providing a unique window into the multifaceted nature of ALS.

The initial model, with an accuracy of 62%, showcases the potential of machine learning in capturing the complexities of ALS diagnosis. However, this highlights the limitations of relying solely on basic clinical data. The remarkable leap to 97% accuracy with the second model, incorporating richer data like family history, functional scores, and genomic information, underscores the critical role of diverse data sources in building robust and accurate models. This aligns with previous research suggesting the promise of genomic data and non-invasive imaging techniques for early detection. However, due to potential overfitting concerns, the more conservative model demonstrating 62% accuracy was favored for its reliability and generalizability. Overfitting can occur when a model memorizes the training data too well, leading to poor performance on unseen data. While the 97% accuracy of the second model is enticing, it might not translate well to real-world clinical settings. Therefore, the 62% model, despite its lower accuracy, offers a more balanced trade-off between accuracy and generalizability, making it a more reliable choice for practical application.

The comparative analysis reveals compelling insights. While the first classifier exhibits moderate performance across all classes, the second classifier displays a remarkable precision and recall (near 1.00) in all categories. This indicates a near-perfect ability to identify both true positives and true negatives, suggesting a highly refined and comprehensive model.

These class-specific performances intimate the need for tailored models or feature sets for different ALS phenotypes. ALS is a heterogeneous disease, with diverse presentations and progression patterns. A single model might not capture the heterogeneity of each phenotype effectively. Therefore, future work will involve refining these models with advanced ML techniques, possibly creating separate models for individual ALS types. This would require careful evaluation of data quality and diversity to address potential biases towards more common presentations.

While this study demonstrates the promise of machine learning for early ALS detection, limitations remain. The moderate initial accuracy necessitates further research to address the disease's inherent heterogeneity and potential data biases. Additionally, the relatively small dataset employed requires validation with larger patient populations that have more racial inclusion to ensure generalizability. Future work should focus on enriching data types with detailed clinical records, longitudinal data tracking disease progression, and exploring advanced feature engineering techniques like dimensionality reduction and feature selection to extract hidden patterns and address data complexity. Additionally, incorporating explainable AI methodologies will be crucial in building transparent and interpretable models for clinical decision-making. Ultimately, continued research in these areas holds immense promise for developing highly accurate and personalized models capable of transforming the landscape of ALS diagnosis and management.

**Conclusion**

This study demonstrates the potential of machine learning for early ALS detection, with significant advancements in model accuracy achieved by incorporating diverse data sources. While limitations remain, including data bias and generalizability, continued research in enriching data types, advanced feature engineering, and explainable AI holds immense promise for developing personalized models and transforming ALS diagnosis and management.

**Reference:**

* Crider, C. (2023, March 21). What are the earliest signs of amyotrophic lateral sclerosis (ALS)?Healthline. <https://www.healthline.com/health/very-early-als-symptoms#at-what-age>
* Fccp, J. J. C. P. B. B. F. (2020, August 25). Overview of current and emerging therapies for amyotrophic lateral sclerosis. AJMC. https://www.ajmc.com/view/overview-of-current-and-emerging-therapies-for-amyotrophic-lateral-sclerosis
* Fukushima, K., Takamatsu, N., Yamamoto, Y., Yamazaki, H., Yoshida, T., Osaki, Y., Haji, S., Fujita, K., Sugie, K., & Izumi, Y. (2022). Early diagnosis of amyotrophic lateral sclerosis based on fasciculations in muscle ultrasonography: A machine learning approach. Clinical Neurophysiology, 140, 136–144. https://doi.org/10.1016/j.clinph.2022.06.005
* Kocar, T. D., Müller, H., Ludolph, A. C., & Kassubek, J. (2021). Feature selection from magnetic resonance imaging data in ALS: a systematic review. Therapeutic Advances in Chronic Disease, 12, 204062232110510. <https://doi.org/10.1177/20406223211051002>
* Naqvi, E. (2019, March 20). ALS Facts and Statistics – ALS News Today. ALS News Today. https://alsnewstoday.com/als-facts-statistics/
* Nathan, R., Miller, C. B., Shukla, O. B., Garbayo, A., Hagan, M. T., Harrison, A., Ciepielewska, M., & Apple, S. (2021). PND53 Predictive Models Leveraging Machine learning and Real-World data for early diagnosis: An application in amyotrophic lateral sclerosis. Value in Health, 24, S169. <https://doi.org/10.1016/j.jval.2021.04.837>
* Phukan J, Elamin M, Bede P, et al. The syndrome of cognitive impairment in amyotrophic lateral sclerosis: a population-based study. J Neurol Neurosurg Psychiatry. 2012;83(1):102-108.​
* Staab W, Balagurusamy VSK, Mlynarski H, et al. Elucidating the Impact of Disease Mutations on Protein Interactome and Function: A Computational Perspective. Front Genet. 2020;11:863.​
* Tena, A., Clarià, F., Solsona, F., & Povedano, M. (2023). Voiceprint and machine learning models for early detection of bulbar dysfunction in ALS. Computer Methods and Programs in Biomedicine, 229, 107309. https://doi.org/10.1016/j.cmpb.2022.107309
* Wang M, Gao J, Yang X, et al. Predicting disease progression in amyotrophic lateral sclerosis: an integrated model based on clinical, biochemical and neurophysiological biomarkers. Neurobiol Aging. 2020;86:101-110.​
* Waller R, Goodall EF, Milo M, et al. Serum miRNAs miR-206, 143-3p and 374b-5p as potential biomarkers for amyotrophic lateral sclerosis (ALS). Neurobiol Aging. 2017;55:123-131.​