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Improving Diagnosis and Prognosis in Hippocampal Sclerosis Epilepsy Through a Multimodal Model

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Abstract The diagnosis of Mesial Temporal Lobe Epilepsy (MTLE) with hippocampal sclerosis (HS) involves a combination of neuroimaging, biomarker analysis, and clinical evaluation. MTLE is the most common form of temporal lobe epilepsy, often associated with HS, which is characterized by neuronal loss and gliosis in the hippocampus. Accurate diagnosis is crucial for effective treatment, often involving surgical intervention. This study aimed to develop and validate a multimodal model for the diagnosis and prognostic evaluation of mesial temporal lobe epilepsy with hippocampal sclerosis.All patients underwent cognitive evaluation with the MoCA and HADS scales, video-EEG monitoring, MMP-9 analyses, and brain MRI in accordance with the HARNESS protocol.Four models were developed on the basis of the integrated analysis of clinical, cognitive, neurophysiological, and biochemical indicators, providing a structured framework for the diagnosis and prognostic evaluation of MTLE-HS.

Keywords Mesial temporal sclerosis, Mesial temporal loe epilepsy with hippocampal sclerosis, Diagnostic model, Matrix metalloproteinase-9, Biomarker

1. Introduction

Mesial temporal lobe epilepsy (MTLE) is the most prevalent and treatment-resistant form of focal epilepsy, representing a major clinical challenge worldwide [1-4]. A substantial proportion of patients with chronic, pharmacoresistant seizures present with hippocampal sclerosis (HS) as the underlying substrate [5,6]. HS is pathologically characterized by selective neuronal loss, gliosis, and synaptic reorganization within the hippocampal formation, particularly in the CA1 and CA3 subfields [7-9]. These structural alterations not only contribute to epileptogenesis but also underlie the cognitive and psychological comorbidities frequently observed in affected patients [10].

Despite significant advances in diagnostic approaches, the reliable identification and prognostic stratification of MTLE-HS remain challenging [11]. Traditional methods such as seizure semiology, long-term video-EEG monitoring, and conventional MRI provide valuable information, yet often fail to fully capture the heterogeneity of disease presentation and outcome [12]. The implementation of standardized MRI protocols, most notably the HARNESS (Harmonized Neuroimaging of Epilepsy Structural Sequences) protocol, has improved the sensitivity and reproducibility of structural imaging in detecting hippocampal sclerosis. HARNESS MRI provides high-resolution and standardized acquisition across centers, enabling more accurate identification of subtle hippocampal changes [13]. However, while neuroimaging remains indispensable, it must be complemented by other modalities to achieve reliable diagnostic and prognostic precision. Beyond imaging, cognitive and psychological assessment offers additional insights into disease burden. Patients with MTLE-HS commonly experience deficits in memory, executive functioning, and emotional regulation, all of which significantly affect quality of life [14,15]. Instruments such as the Montreal Cognitive Assessment (MoCA) and the Hospital Anxiety and Depression Scale (HADS) allow systematic evaluation of these domains [16]. Yet, these measures have rarely been incorporated into integrated predictive models of MTLE-HS.

Emerging biochemical biomarkers provide another promising avenue. Among them, matrix metalloproteinase-9 (MMP-9) has gained increasing attention due to its involvement in extracellular matrix remodeling, blood–brain barrier disruption, and neuroinflammatory processes—all of which are implicated in epileptogenesis and seizure recurrence [17,18]. Elevated serum MMP-9 levels have been observed in patients with temporal lobe epilepsy, but its potential as part of a multimodal diagnostic and prognostic framework remains insufficiently explored [5,19].

Considering the multifactorial nature of MTLE-HS, there is a strong rationale for developing multimodal approaches that integrate clinical, cognitive-psychological, electrophysiological, biochemical, and advanced neuroimaging data. Such models have the potential not only to improve

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diagnostic accuracy but also to stratify patients according to risk, predict disease course, and guide treatment strategies, including surgical interventions.

In this study, we systematically assessed patients with MTLE-HS using a comprehensive battery comprising clinical-semiological evaluation, long-term video-EEG monitoring, standardized cognitive and psychological testing, biochemical assays with MMP-9 measurement, and brain MRI performed in accordance with the HARNESS protocol. Based on the integrated analysis of these multidimensional datasets, we developed and validated a multimodal prognostic model and diagnostic algorithm designed to enhance diagnostic precision and individualized prognostication in MTLE-HS.

2. Materials and Methods

This analytical cross-sectional study was conducted between 2023 and 2025 at two clinical sites: the Department of Neurology, Clinical Hospital No. 1 of Tashkent State Medical University (TSMU), and the Central District Polyclinic of Khatirchi. A purposive sampling strategy was applied, and a total of 88 participants were enrolled. Subjects were divided into three groups: the main group (n = 30), consisting of patients diagnosed with mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS) according to the International League Against Epilepsy (ILAE) 2017 criteria; the comparative group (n = 36), including patients with other forms of epilepsy but without hippocampal sclerosis on MRI; and the control group (n = 22), comprising neurologically healthy individuals without epilepsy or structural brain pathology.

All participants underwent structured clinical and semiological evaluation. Cognitive and psychological status was assessed using the Montreal Cognitive Assessment (MoCA) and the Hospital Anxiety and Depression Scale (HADS). Long-term video-EEG monitoring was performed for all patients in the epilepsy groups. Brain MRI was carried out in accordance with the standardized HARNESS (Harmonized Neuroimaging of Epilepsy Structural Sequences) protocol to evaluate structural alterations, particularly hippocampal sclerosis. Peripheral venous blood samples were collected from all participants via the antecubital vein, and serum was analyzed for biochemical marker, matrix metalloproteinase-9 (MMP-9).

All data were statistically processed using the DataTab online platform. Based on the results of statistical analysis, four analytical modules were constructed: clinical-semiological, cognitive-psychological, EEG, and biochemical.

3. Results and Discussion

The alterations of the MMP-9 biomarker in mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS) and its relationship with age and sex factors were investigated. The analysis demonstrated significant intergroup and sex-related differences in MMP-9 levels among patients with MTLE-HS. In the main group, the mean serum MMP-9 concentration was 71.27 ±22.82 ng/ml, which was markedly higher compared with both the comparative group (patients with MTLE without hippocampal sclerosis) and the control group (healthy individuals), where the mean values were 31.76 ± 19.32 ng/ml and 18.63 ± 3.07 ng/ml, respectively (Table 1).

Table 1. Descriptive statistics of study variables across groups

	Group	Sex	Frequency	%	Mean ± Std.deviation
MMP9_ngmL	Comparing	Male	16	18,18%	37,22 ±26,21
		Female	20	22,73%	27,4 ±10,03
	Main	Male	18	20,45%	65,94 ±15,37
		Female	12	13,64%	79,27 ±29,85
	Control	Male	9	10,23%	17,1 ±3,14
		Female	13	14,77%	19,69 ±2,64

Table 2. LASSO regression coefficients of clinical predictors influencing MMP-9 levels

Clinical variable	Unstandardized B coefficient	Standardized β coefficient
Initial precipitating injury	19,62	9,70
Postictal confusion	13,70	6,73
Presence of aura	11,63	5,77
Ictal speech arrest	5,60	2,29
Automatism	4,63	2,29
Autonomic disturbances	4,93	2,27
Constant (intercept)	22,69	–

Table 3. Diagnostic modules, predictors, weights, and performance indices

Module	Key Predictors (Auxiliary Score Formula)	AUC	Weight
Clinical-semiological	Aura, speech arrest, automatisms, initial precipitating injury (IPI) → (Aura + Speech + Automatisms + IPI) × 0.25	0.868	1.0
Cognitive-psychological	MoCA < 26, HADS-Anxiety > 10 → (Low MoCA + High Anxiety) × 0.5	0.785	0.75
EEG	TIRDA, PLED, or background slowing → 1 (if present)	0.822	0.9
Biochemical (MMP-9)	MMP-9 > 60 ng/mL → 1	0.947	1.25

To determine the influence of various clinical factors on MMP-9 levels, a LASSO regression analysis was performed using standardized independent variables. The analysis revealed that the presence of an initial precipitating injury (IPI), postictal confusion, and aura were the strongest predictors of elevated MMP-9 levels. Table 2 summarizes the clinical variables that showed a significant effect on MMP-9 concentration together with their regression coefficients.

A strong and statistically significant inverse correlation was found between MoCA scores and MMP-9 levels ($r(28) = -0.75$, $p < 0.001$). Higher MoCA scores, indicating better cognitive function, were associated with lower MMP-9 concentrations, whereas elevated MMP-9 was linked to greater cognitive decline. Consistent with this, both Spearman and linear regression analyses revealed a moderate positive correlation between HADS-Anxiety scores and MMP-9 levels ($r(28) = 0.53$, $p = 0.003$; Fig. 1), with regression confirming anxiety as a significant predictor ($R^2 = 0.23$; $B = 3.88$; $p = 0.007$). By contrast, HADS-Depression scores showed only a weak and non-significant association with MMP-9 ($r = 0.15$, $p = 0.423$). These results suggest that MMP-9 may represent a biomarker of cognitive impairment in MTLE-HS, while also reflecting anxiety-related, but not depressive, psychopathology, underscoring potentially distinct neurobiological mechanisms. Multivariate linear regression analysis indicated that the presence of TIRDA, PLED, and slow waves on EEG were evaluated as predictors of MMP-9 levels. The model was statistically significant ($F(3,62) = 3.32$; $p = 0.025$), accounting for 14% of the variance ($R^2 = 0.14$). Among the predictors, only TIRDA showed a statistically significant effect on MMP-9 concentrations ($B = 20.9$; $p = 0.016$), suggesting an association between TIRDA and elevated MMP-9 levels. Furthermore, Spearman correlation analysis revealed a strong positive and statistically significant relationship between the severity of MTS and MMP-9 concentrations ($r(28) = 0.86$; $p < 0.001$), indicating that higher clinical grades of MTS are associated with markedly increased MMP-9 levels.

A multimodular diagnostic model was developed to enable the early and accurate identification of mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS). The model integrated four domains: clinical, cognitive-psychological, electroencephalographic, and biochemical. Each domain contributed an auxiliary score based on statistically validated predictors derived from logistic regression, and the diagnostic performance of each module was evaluated using the area under the receiver operating characteristic curve (AUC), reflecting sensitivity and specificity. The clinical-semiological module (AUC = 0.868, weight = 1.0) included key predictors such as aura, ictal speech arrest, automatisms, and a history of initial precipitating injury (IPI), all of which are typical clinical markers of MTLE-HS. Each feature was assigned one point, and the auxiliary score was calculated accordingly. The cognitive-psychological module (AUC = 0.785, weight = 0.75) was based on the presence of cognitive and emotional dysfunction, with predictors including Montreal Cognitive Assessment (MoCA) scores below 26 and HADS-Anxiety scores greater than 10. Each criterion contributed one point, forming the auxiliary score. The EEG module (AUC = 0.822, weight = 0.9) incorporated the presence of characteristic electrophysiological abnormalities such as TIRDA, PLED, or background slowing.

The auxiliary score was assigned if at least one of these features was detected. The biochemical module, represented by MMP-9 (AUC = 0.947, weight = 1.25), demonstrated the highest diagnostic accuracy. MMP-9 levels greater than 60 ng/mL were identified as the strongest predictor, and the auxiliary score was defined on this basis. The final diagnostic index was derived by multiplying each auxiliary score by its respective weight and normalizing the result to a 0–5 scale.

Risk categories were defined as follows: scores between 0.0 and 1.9 indicated low risk, where alternative etiologies should be considered and neurological consultation or re-evaluation may be required; scores between 2.0 and 2.9 reflected moderate risk, suggesting the need for additional testing, including MRI, video-EEG, and neuropsychological assessment; scores of 3.0 or higher indicated high risk, warranting comprehensive differential diagnosis. In high-risk cases, further structural assessment using 3T HARNESS-MRI, functional evaluation with video-EEG, biomarker confirmation (if MMP-9 sampling was performed within the past 1–2 months), and treatment planning, including antiepileptic drug optimization or surgical evaluation, were recommended (Table 3, Figure 1.).

This modular scoring system provides a validated framework for quantifying disease probability and guiding clinical decision-making in MTLE-HS.

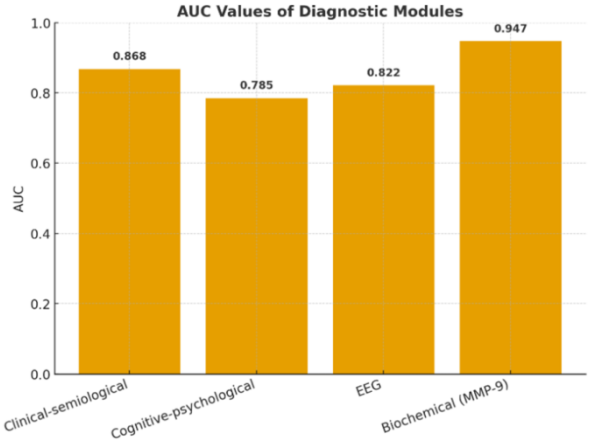

Figure 1. AUC values of diagnostic modules

4. Conclusions

This study demonstrates that a multimodular diagnostic model integrating clinical semiological features, cognitive-psychological indicators, EEG abnormalities, and the biochemical biomarker MMP-9 offers a systematic and reliable approach to the early identification of mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS). Each module contributes an independent auxiliary score, with diagnostic performance validated by AUC indices and statistically significant predictors. The weighted composite scoring system enables precise risk stratification into low, moderate, and high categories, each associated with tailored recommendations for further diagnostic testing and individualized treatment planning. Beyond improving diagnostic accuracy, the modular framework provides practical advantages for clinical practice by optimizing resource utilization, facilitating earlier detection, and supporting personalized therapeutic strategies. These findings underscore the potential of this integrated approach to improve outcomes in patients with MTLE-HS and highlight the need for validation in larger, multicenter cohorts.

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