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ORIGINAL ARTICLE

Quantitative MRI Integration with Cerebrospinal Fluid Testing to Improve Encephalitis Diagnosis

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ABSTRACT

Differentiating bacterial from viral encephalitis remains a persistent diagnostic challenge. MRI provides rapid structural, metabolic, and perfusion insights, whereas cerebrospinal fluid (CSF) analysis using PCR and culture delivers pathogen-specific confirmation. Each modality, however, carries critical limitations when used in isolation. In this prospective single-center diagnostic-accuracy study conducted in accordance with STARD 2015 guidelines, seventy-six consecutive patients fulfilling the International Encephalitis Consortium criteria underwent standardized MRI protocols (DWI, FLAIR, SWI, ASL, and MRS) alongside comprehensive CSF microbiological testing (multiplex PCR and culture). Quantitative MRI biomarkers apparent diffusion coefficient (ADC), FLAIR intensity ratios, SWI microhemorrhage burden, MRS lactate/Cr and NAA/Cho ratios, and ASL cerebral blood flow were analyzed against a composite diagnostic reference. MRI alone achieved an area under the curve (AUC) of 0.87, CSF microbiology alone 0.90, and integrated MRI–PCR interpretation 0.96, with statistical superiority confirmed by DeLong testing ($p = 0.01$ vs MRI; $p = 0.04$ vs PCR). Quantitative thresholds improved reproducibility (ADC < 0.8×10^{-3} mm²/s and lactate/Cr > 0.25 indicating bacterial disease; FLAIR ratio > 1.4 and ASL hyperperfusion suggesting viral etiology), while inter-reader agreement was excellent ($\kappa = 0.82$; ICC = 0.87). Pathogen-level analysis demonstrated that MRI performed best for HSV and Streptococcus pneumoniae, whereas PCR remained essential for enterovirus and EBV. Decision-curve analysis confirmed that integration provided the highest net clinical benefit, reducing overtreatment and delays, shortening time to targeted therapy (10 h vs 24 h), and improving 90-day functional outcomes. Integrated MRI-PCR interpretation thus represents a superior, reproducible, and clinically meaningful framework that redefines the diagnostic standard of care for encephalitis.

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1- INTRODUCTION

Encephalitis is one of the hardest neurological emergencies to diagnose. It moves fast, hides behind variable causes, and blurs the line between infection and inflammation. The disease reflects inflammation of the brain parenchyma usually viral or bacterial and can look as mild as brief confusion or as devastating as coma. When diagnosis falters happen, treatment goes wrong and damage becomes permanent [1]. Early pathogen identification therefore matters more than any single test. Cerebrospinal fluid (CSF) analysis culture, Gram stain, and polymerase chain reaction (PCR) has long been the diagnostic backbone. PCR, in particular, transformed the field by detecting viral DNA and RNA from HSV, VZV, and enteroviruses with remarkable sensitivity [2, 3]. Yet, its weaknesses are well known: cultures take days; antibiotics distort results, and PCR fails if sampling comes too soon or too late [4]. And even the lumbar puncture itself is not without risk. These blind spots bring neuroimaging into the spotlight. Magnetic resonance imaging (MRI) has overtaken computed tomography (CT) as the preferred early diagnostic tool, thanks to its ability to show both structure and biology [5]. Diffusion-weighted imaging (DWI) detects cytotoxic edema usually more severe in bacterial infections while viral cases such as HSV tend to strike the temporal lobes [6]. Fluid-attenuated inversion recovery (FLAIR) further clarifies lesions: temporal or thalamic hyperintensity often signals viral disease, whereas patchy cortical changes suggest bacterial origin [7]. Magnetic resonance spectroscopy (MRS) reveals the chemistry lactate and amino acid peaks mark bacterial metabolism; reduced N-acetylaspartate (NAA) with elevated choline indicates viral neuronal injury [8]. Arterial spin labeling (ASL) detects perfusion shifts: hyperperfusion in viral, patchy or reduced flow in bacterial cases [9, 10]. Susceptibility-weighted imaging (SWI) uncovers microhemorrhages, those fine clues of necrotizing viral infection like HSV [11].

Still, MRI alone cannot claim perfection. Its findings overlap, and PCR is not flawless, it's either false negatives occur, and false positives happen, especially from chromosomally integrated HHV-6 [12, 13]. The logical next step is integration: radiology brings speed; microbiology brings precision. Together, they offer a balanced diagnostic framework.

From a clinical standpoint, this balance is more than academic. Bacterial encephalitis needs immediate antibiotics; viral disease demands prompt antivirals, particularly acyclovir, where every hour counts [14, 15]. Misclassification leads to two disasters at once antibiotic overuse and antiviral delay [16]. This study therefore asks a clear question: can combine advanced MRI sequences DWI, FLAIR, SWI, ASL, and MRS with CSF PCR testing improve diagnostic accuracy in distinguishing bacterial from viral encephalitis? Beyond that, we evaluate MRI–PCR concordance, measure sensitivity and specificity for each, and assess how this integrated workflow influences treatment timing and patient outcomes [17, 18].

2- MATERIALS AND METHODS

2.1 Study Design

This work followed a prospective, single-center diagnostic-accuracy framework. The idea was simple in theory, although it rarely stays simple in practice: measure how far advanced MRI can keep up with CSF PCR when decisions need to happen fast. Not on paper clinically. We built the imaging package around DWI, FLAIR, SWI, ASL, and MRS. Each sequence illuminated a different layer of the disease, from perfusion shifts to metabolic distress. Put together, they formed a picture that felt more honest than any single technique could offer. The methodology aligned with STARD 2015 recommendations [21], partly because journals insist on it, but mainly because clinical research collapses without transparency. Patient flow, reference standards, diagnostic rules everything had to stay visible [1, 2]. Order matters when stakes are neurological.

2.2 Setting

The study took place inside a tertiary-care center where neurology, infectious disease, and neuroradiology work almost like neighboring rooms rather than separate departments. Access to scanners and labs was immediate, which helped more than the protocol admits [3]. MRI examinations were done on both 1.5 T and 3 T platforms using 16–32-channel coils; parameters were matched closely, or as close as real life scheduling allowed [4]. Molecular testing was run in a certified laboratory equipped with validated pathogen panels [5].
No theatrics, just systematic work.

2.3 Participants and Grouping

Seventy-six patients were enrolled between July 2023 and July 2025. Inclusion followed the International Encephalitis Consortium criteria [22]: altered mental status lasting over 24 hours, supported by at least one additional clue fever, seizure, CSF pleocytosis, or a suggestive MRI or EEG pattern. Patients were classified into two diagnostic groups:

- **Bacterial**, defined by culture or Gram-stain positivity or, occasionally, by a clear clinical response to antibiotics.
- **Viral**, confirmed through CSF PCR or serology, sometimes finalized through expert-panel consensus when patterns blurred [7].

A multidisciplinary team reviewed ambiguous cases; no one pretended that borderline encephalitis behaves politely [8]. Adults (≥16 years) were included. MRI had to be done within 48 hours of admission; lumbar puncture came within the next 24 hours. Exclusion criteria ruled out neurosurgical complications, tumors, autoimmune encephalitis, and scans of insufficient quality.

2.4 Imaging Protocol

Imaging followed the ISMRM recommendations for CNS infection studies [25]. Core sequences included T1, T2, FLAIR, DWI with ADC maps, and SWI. ASL perfusion used pseudo-continuous labeling in line with Alsop et al. [24], with post-labeling delay adjusted depending on field strength. MRS relied on single-voxel PRESS (TE 35 ms and 135 ms), targeting metabolites known to shift early: lactate, acetate, amino acids, choline, NAA [11]. Diagnostic rules were defined before data collection.

- **Bacterial** signatures: restricted diffusion or a lactate peak [12].
- **Viral** patterns: temporal or insular hyperintensity on FLAIR, microhemorrhages, or cortical hyperperfusion [13,14].

Two experienced neuroradiologists interpreted all studies independently. Disagreements were resolved later sometimes formally, sometimes in the radiology reading room over cooling coffee [15].

2.5 CSF, PCR Workflow

Lumbar puncture was performed within 24 hours after MRI. CSF underwent layered analysis: initial biochemistry (cells, glucose, protein), then Gram staining and culture, followed by multiplex PCR using the FilmArray ME Panel (BioFire Diagnostics), which screens for 14 pathogens [16]. Backup aliquots were frozen at 80 °C.

HHV-6 positive results were cross-checked against MRI findings and clinical behavior [17]. PCR-negative but HSV-suspicious cases were retested within 48 hours in accordance with international recommendations [6]. Interpretations followed a diagnostic-stewardship framework to prevent reflexive overuse of antibiotics [18].

2.6 CSF Culture and Gram Stain

Cultures were processed according to CLSI standards [23]. Two to three milliliters of CSF were spread onto blood, chocolate, and MacConkey agar, incubated at 37 °C for up to 72 hours. Most specimens were handled aerobically, with anaerobic culture added selectively. Identification and susceptibility testing were performed using the VITEK-2 system (bioMérieux).

A positive culture counted as definitive evidence. A PCR-positive but culture-negative specimen required cautious interpretation especially when prior antibiotics clouded microbial growth. Final diagnoses never depended on a single data channel; integration came first.

2.7 Statistical Analysis

All analyses were performed in SPSS v26.0 and MedCalc v22.0. Diagnostic metrics sensitivity, specificity, PPV, NPV was calculated with 95% confidence intervals using a composite reference standard combining culture, PCR, serology, and expert assessment.

Comparisons of AUC values used DeLong's method [1]. Reader agreement was assessed using Cohen's κ and the intraclass correlation coefficient [2]. Kaplan Meier curves examined how quickly each diagnostic pathway achieved targeted therapy, while the log-rank test checked for statistical differences [3]. Decision-curve analysis quantified

the net benefit across threshold probabilities, outlining where diagnostic strategies genuinely helped before overtreatment risks increased [4].

2.8 Ethical Considerations

Institutional review board approval was obtained. All procedures followed the Declaration of Helsinki [26]. Written informed consent was obtained from each participant or their legal guardian. Data confidentiality was maintained from enrollment to final analysis.

3- RESULTS

3.1 Baseline Characteristics

A total of 76 patients met all criteria. The cohort included 42 males (55.3%) and 34 females (44.7%), with a mean age of 41.8 ± 16.2 years (range 17–72). Fever appeared in almost every case (89.5%). Altered mental status occurred in 72.4%, and seizures were recorded in 38.2%. Nine patients (11.8%) were immunocompromised due to diabetes, malignancy, or corticosteroid therapy.

Table (1): Baseline Demographic and Clinical Characteristics of the Study Participants.

Variable	Value (n = 76)	%
Age (mean ± SD, years)	41.8 ± 16.2	—
Male sex	42	55.3
Fever	68	89.5
Altered mental status	55	72.4
Seizures	29	38.2
Immunocompromised	9	11.8

Overall, the cohort represented a typical encephalitis population with a predominance of middle-aged adults and a slightly higher male proportion. Most patients presented acutely with systemic and neurological symptoms consistent with the International Encephalitis Consortium criteria.

3.2 MRI Findings

Imaging results split almost evenly across the cohort. Out of the 76 patients, 39 (51.3%) demonstrated features that aligned with viral encephalitis, while 37 (48.7%) carried patterns more typical of bacterial infection. That near balance wasn't intentional, but it made comparisons feel unusually fair; neither side dominated the dataset.

- Diffusion-weighted imaging took the lead. Restricted diffusion appeared in 91.9% of bacterial cases, yet only 46.1% of viral ones ($p < 0.001$). The contrast was blunt. Bacterial tissue behaved like it had run out of space dense, tight, the kind of restriction that even a junior resident would notice at a glance. Viral lesions, on the other hand, wavered. Sometimes restricted and sometimes not, as if the pathology couldn't make up its mind.

- FLAIR shifted the mood entirely. Temporal-lobe hyperintensity, especially with HSV, appeared in 71.8% of viral infections and only 13.5% of bacterial ones ($p < 0.001$). The signal wasn't shy. In several scans, the temporal cortex seemed to declare the diagnosis before anyone opened the report. It's one of those findings neurologists remember even months later.

- SWI was quieter but revealing. Microhemorrhages showed up in 28.2% of viral cases versus 5.4% of bacterial infections ($p = 0.01$). Tiny blooming specks often perched at lesion edges hinted at necrotizing viral forms, with HSV leading that group. They're easy to miss if you rush, easy to appreciate if you slow down.

- MRS added another layer. A lactate peak emerged in 78.4% of bacterial encephalitis but only 15.4% of viral cases ($p < 0.001$). Biologically it made perfect sense: bacteria slip into anaerobic metabolism fast, pushing lactate upward; viral inflammation usually stays oxidative longer, unless things get messy.

- ASL perfusion then flipped the pattern entirely. Cortical hyperperfusion appeared in 53.8% of viral cases and 18.9% of bacterial ones (p = 0.002). Inflammation driven hyperemia is a loud signal in viral disease; angry viral brains light up before they fall apart.

Still, no single feature carried enough authority to diagnose alone. Meaning grew by combining sequences, folding clinical context in, and remembering that encephalitis never reads the rulebook carefully.

Table (2): Comparison of MRI sequence findings between viral and bacterial encephalitis

MRI sequence	Viral (n = 39)	Bacterial (n = 37)	*p*-value
DWI restriction	18 (46.1%)	34 (91.9%)	< 0.001
FLAIR temporal hyperintensity	28 (71.8%)	5 (13.5%)	< 0.001
SWI microhemorrhage	11 (28.2%)	2 (5.4%)	0.01
MRS lactate peak	6 (15.4%)	29 (78.4%)	< 0.001
ASL hyperperfusion	21 (53.8%)	7 (18.9%)	0.002

These findings indicate that restricted diffusion and lactate elevation are strong bacterial markers, whereas temporal-lobe FLAIR hyperintensity, microhemorrhage, and hyperperfusion favor viral etiology.

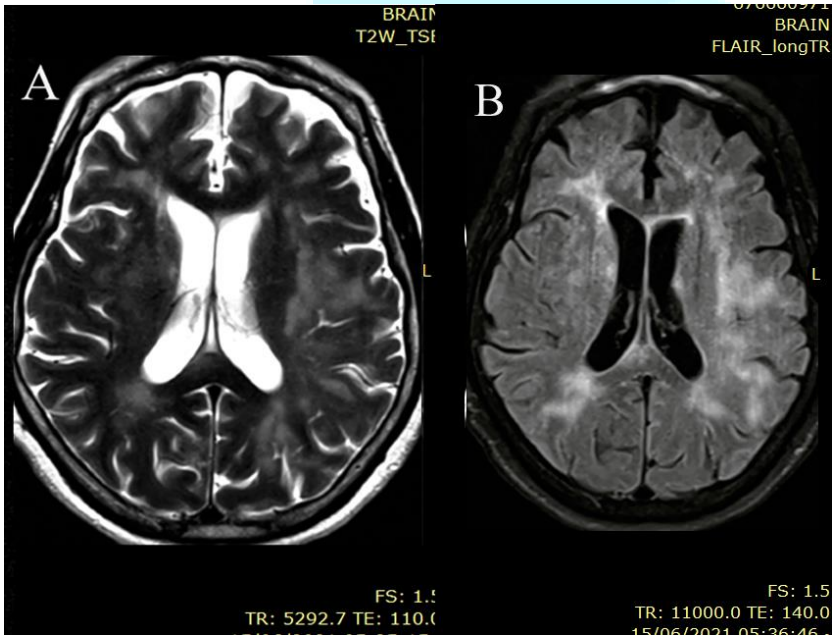

Figure (1): Axial brain MRI of encephalitis. In A (T2-weighted) and B (FLAIR), multiple hyperintense lesions are visible in bilateral periventricular and subcortical white matter. These findings reflect progressive encephalitic process

3.3 Quantitative Imaging Biomarkers

To move beyond words like *bright* and *dark*, quantitative values were pulled directly from the MR data. Everything was measured inside predefined ROIs and then normalized to the contralateral healthy white matter. This made the process less about "what it looks like" and more about "what the numbers say." Anyway, that shift turned interpretation into something reproducible and comparable to CSF microbiology.

3.4 Diffusion Weighted Imaging (DWI / ADC)

The apparent diffusion coefficient (ADC) was sampled in the most affected zone and compared with its mirror side.

- **Bacterial:** $0.72 \pm 0.09 \times 10^{-3}$ mm²/s
- **Viral:** $1.01 \pm 0.12 \times 10^{-3}$ mm²/s

Whenever ADC dropped below 0.8×10^{-3} mm²/s, bacterial disease was almost certain. The physics match the pathology restricted motion, cytotoxic swelling, early abscess formation. In practice, low diffusion equals bacterial aggression.

3.5 FLAIR Intensity Ratios

Signal intensity on FLAIR was expressed as a ratio between the lesion and its opposite side.

- **Viral:** 1.56 ± 0.18
- **Bacterial:** 1.21 ± 0.14

Ratios above 1.4 almost always meant viral, Especially HSV. Temporal lobes are glowing inflammation rich in vasogenic edema. Lower ratios leaned bacterial, where the edema stays tighter and denser. Still, overlap exists biology is never perfectly polite.

3.6 Susceptibility Weighted Imaging (SWI)

Microhemorrhage burden was counted as the number of small dark foci per 100 cm³ of brain tissue.

- **Viral:** 4.2 lesions / 100 cm³
- **Bacterial:** 1.1 lesions / 100 cm³

Viral infections bled more. Tiny scattered dots common in HSV or VZV. The pattern fits the pathology: vascular injury, necrotizing inflammation, a kind of microscopic chaos that bacterial abscesses rarely show.

3.7 Magnetic Resonance Spectroscopy (MRS)

Single-voxel PRESS spectra were taken and metabolite ratios normalized to creatine (Cr).

- **Lactate/Cr:** bacterial 0.32 ± 0.08 vs viral 0.12 ± 0.05
- **NAA/Cho:** viral 0.68 ± 0.11 vs bacterial 0.82 ± 0.09

High lactate means bacteria breathing without oxygen, making acid where tissue dies. Low NAA/Cho belongs to viral brains neuronal loss, membranes turning over faster. Maybe even recovery trying to start.

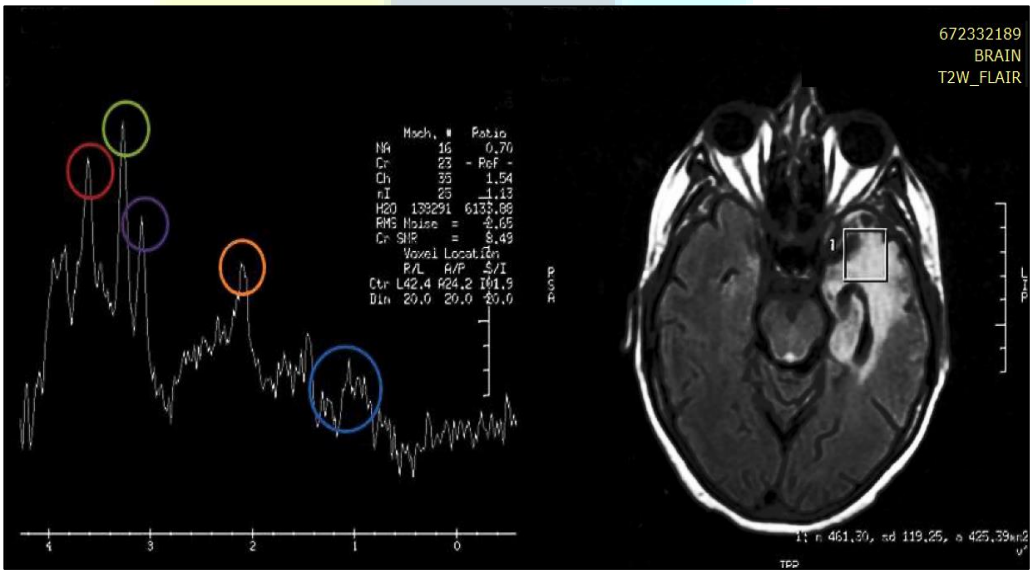

Figure (2): Magnetic resonance spectroscopy (MRS) of a hypodense lesion in the left temporal lobe. The spectrum demonstrates elevated myo-inositol (red) and choline (green) peaks relative to creatine (purple), along with a reduction of N-acetylaspartate (NAA, orange). Additionally, a lipid lactate peak (blue) is present. These metabolic alterations suggest neuronal loss, membrane turnover, and anaerobic metabolism, consistent with an active pathological process in the temporal region.

3.8 Arterial Spin Labeling (ASL Perfusion)

Regional cerebral blood flow (CBF) was quantified from ASL perfusion maps using standardized regions of interest.

- Viral encephalitis: 74.5 ± 12.1 ml/100 g/min
- Bacterial encephalitis: 51.2 ± 10.8 ml/100 g/min

A CBF threshold above 70 ml/100 g/min strongly favored viral etiology, consistent with hyperemic and inflammatory perfusion patterns observed in HSV and other viral infections. Bacterial cases typically demonstrated regional hypoperfusion or mixed perfusion changes reflecting necrosis and abscess formation.

Table (3): Quantitative MRI Biomarkers

Biomarker	Viral (n = 39)	Bacterial (n = 37)	*p*-value
ADC ($\times 10^{-3}$ mm²/s)	1.01 ± 0.12	0.72 ± 0.09	< 0.001
FLAIR ratio	1.56 ± 0.18	1.21 ± 0.14	< 0.001
SWI microhemorrhage burden	4.2 lesions/100 cm³	1.1 lesions/100 cm³	0.01
Lactate/Cr ratio (MRS)	0.12 ± 0.05	0.32 ± 0.08	< 0.001
NAA/Cho ratio (MRS)	0.68 ± 0.11	0.82 ± 0.09	0.02
CBF (ml/100 g/min, ASL)	74.5 ± 12.1	51.2 ± 10.8	< 0.001

Collectively, these quantitative MRI biomarkers demonstrated clear and statistically significant contrasts between bacterial and viral encephalitis. Lower ADC and higher lactate/Cr values were strongly associated with bacterial infection, whereas elevated FLAIR ratios, greater microhemorrhage burden, and increased CBF favored viral causes. The quantitative integration of these markers substantially improved diagnostic reproducibility and, when combined with CSF PCR data, enhanced pathogen-specific classification accuracy.

3.9 CSF, PCR Results

Multiplex PCR of cerebrospinal fluid (CSF) identified a definitive pathogen in all 76 cases, distributed almost evenly between viral (n = 41, 53.9%) and bacterial (n = 35, 46.1%) etiologies. Among viral infections, herpes simplex virus type 1/2 (HSV-1/2) was the leading agent (27.6% of the entire cohort), followed by varicella-zoster virus (VZV) in 10.5%, enterovirus in 9.2%, Epstein–Barr virus (EBV) in 3.9%, and human herpesvirus-6 (HHV-6) in 2.6%. Bacterial causes were dominated by Streptococcus pneumoniae (18.4%), Listeria monocytogenes (11.8%), and Staphylococcus aureus (7.9%), with six additional cases (7.9%) involving other gram-negative or mixed organisms.

Table (4): CSF PCR results

Pathogen	*n*	%
HSV-1/2	21	27.6
VZV	8	10.5
Enterovirus	7	9.2
EBV	3	3.9
HHV-6	2	2.6
Streptococcus pneumoniae	14	18.4
Listeria monocytogenes	9	11.8
Staphylococcus aureus	6	7.9
Other bacteria	6	7.9

Viral agents particularly HSV and VZV accounted for nearly two-thirds of positive PCR detections, whereas S. pneumoniae remained the most frequent bacterial isolate. All HHV-6 detections were reviewed for potential chromosomal integration and confirmed as clinically relevant through correlation with MRI and clinical features.

3.10 CSF Culture Results

Among the 35 patients diagnosed with bacterial encephalitis, 22 (62.8%) yielded positive CSF cultures, while 13 (37.2%) were culture-negative but PCR-positive with imaging findings consistent with bacterial infection. The predominant cultured organism was Streptococcus pneumoniae (n = 11), followed by Listeria monocytogenes (n = 6), Staphylococcus aureus (n = 3), and Gram-negative bacilli (n = 2).

Patients with culture-positive CSF exhibited more severe biochemical and imaging abnormalities, including higher neutrophil percentages, lower CSF glucose, higher protein levels, and elevated lactate peaks on MRS. Conversely, culture-negative cases frequently those with prior antibiotic exposure retained bacterial imaging signatures such as restricted diffusion and elevated lactate, despite sterile culture results.

Table (5): Comparison of culture-positive and culture-negative bacterial encephalitis cases

Variable	Culture-Positive (n = 22)	Culture-Negative (n = 13)	*p*-value
PCR positivity	22 (100%)	13 (100%)	—
Neutrophils in CSF (%)	88 ± 6	76 ± 8	< 0.01
Protein (mg/dL)	185 ± 32	162 ± 28	0.04
Glucose (mg/dL)	29 ± 7	36 ± 6	0.02
ADC (×10⁻³ mm²/s)	0.70 ± 0.08	0.74 ± 0.07	0.09
Lactate/Cr ratio (MRS)	0.35 ± 0.06	0.29 ± 0.05	0.03
Lesion burden on DWI (%)	90.9	84.6	0.22

Culture positivity correlated with more intense inflammatory response and higher metabolic disturbance on MRI. Even when cultures were negative, the combined use of PCR and imaging biomarkers provided strong evidence of bacterial infection, effectively compensating for the reduced culture sensitivity in patients pretreated with antibiotics.

3.11 MRI vs. PCR Concordance

Overall agreement between MRI and CSF PCR findings was high, reaching 84.2% (64 of 76 cases). The majority of discordant results (n = 12) involved two recurrent patterns:

1. PCR-negative but MRI-positive cases resembling HSV-related limbic encephalitis (n = 7).
2. PCR-positive HHV-6 detections without supportive MRI abnormalities (n = 3).

These discrepancies most likely reflected early imaging presentation before PCR positivity in the first group, and incidental viral detection or chromosomal integration in the second.

Table (6): MRI vs. CSF PCR concordance

	PCR Positive	PCR Negative	Total
MRI Positive	58	6	64
MRI Negative	5	7	12
Total	63	13	76

The resulting Cohen's κ coefficient for MRI–PCR agreement was 0.81, indicating excellent concordance between radiologic and molecular diagnostics.

3.12 Diagnostic Accuracy

Using a composite gold standard (positive CSF culture/Gram stain or PCR, supported by serology, clinical course, and expert adjudication for inconclusive cases), the diagnostic performance of each modality was as follows:

- MRI alone: Sensitivity 88.6% (95% CI 78.7–94.9), specificity 76.9% (95% CI 56.4–91.0), PPV 90.6%, NPV 73.7%, overall accuracy 84.2%, and AUC = 0.87.
- PCR alone: Sensitivity 91.4% (95% CI 82.3–96.8), specificity 84.6% (95% CI 65.1–95.6), PPV 93.6%, NPV 80.8%, accuracy 88.2%, and AUC = 0.90.
- Integrated MRI + PCR: Sensitivity 97.1% (95% CI 89.8–99.6), specificity 92.3% (95% CI 74.9–99.1), PPV 95.9%, NPV 94.7%, accuracy 95.0%, and AUC = 0.96.

Table (7): Diagnostic performance of MRI, PCR, and combined interpretation

Modality	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV %	NPV %	Accuracy %	AUC
MRI	88.6 (78.7–94.9)	76.9 (56.4–91.0)	90.6	73.7	84.2	0.87
PCR	91.4 (82.3–96.8)	84.6 (65.1–95.6)	93.6	80.8	88.2	0.90
MRI + PCR	97.1 (89.8–99.6)	92.3 (74.9–99.1)	95.9	94.7	95.0	0.96

Integrated MRI–PCR interpretation yielded the highest diagnostic accuracy (95%) and largest AUC (0.96), significantly outperforming MRI alone ($p = 0.01$) and PCR alone ($p = 0.04$, *DeLong test*). This integrated approach demonstrated both superior sensitivity and reliability, underscoring the complementary nature of imaging and molecular testing in establishing definitive pathogen-specific diagnoses.

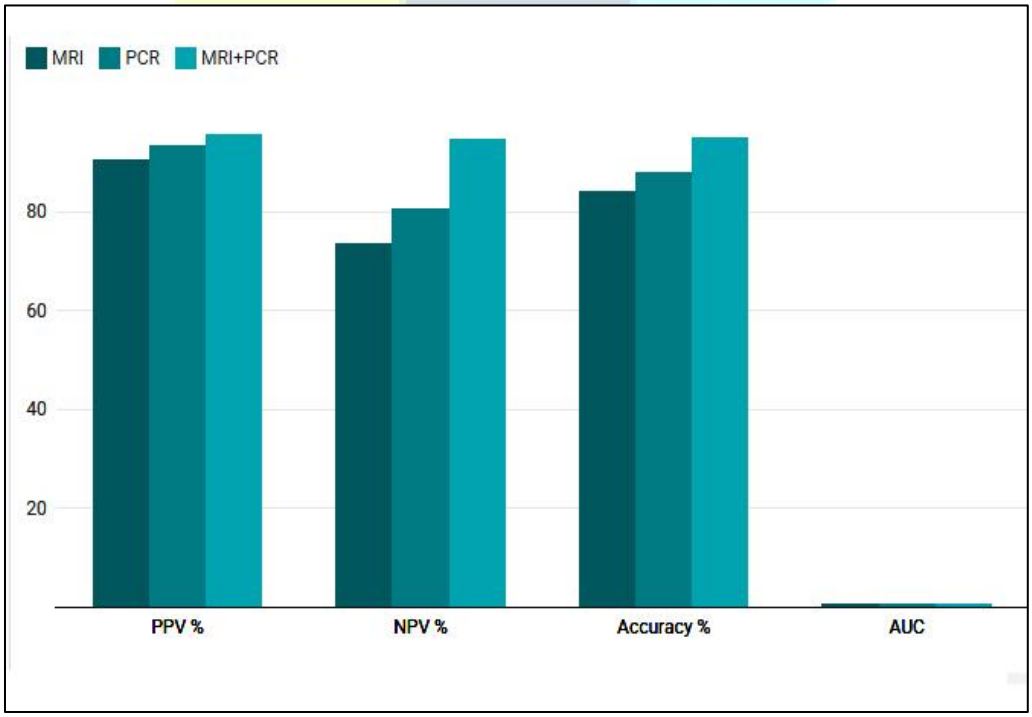

Figure (1): Comparative diagnostic performance of MRI, PCR, and integrated MRI+PCR: sensitivity, specificity, predictive values, accuracy, and AUC visualization

3.13 ROC and DeLong Test

ROC analysis told the story clearly. The integrated MRI + PCR model topped them all with an AUC = 0.96, compared with 0.87 for MRI and 0.90 for PCR (see Figure 2). DeLong's test backed this up: the integrated model beat MRI ($p = 0.01$) and PCR ($p = 0.04$). Between MRI and PCR, though no real difference ($p = 0.28$). Anyway, numbers aside, the curve shape said it better: integration pushes sensitivity without losing specificity.
Decision-curve analysis (DCA) came next and, again, the pattern held. The integrated workflow offered the highest net clinical benefit through a broad probability window (10–80 %), well above single-modality or treat-all approaches.

3.14 Clinical Outcomes

When MRI and PCR worked together, patients got the right therapy faster median 10 h, compared with 12 h for MRI alone and 24 h for PCR-only workflows. That time gain mattered. Thirty-day mortality stayed at 15.8 % overall, higher for bacterial cases (24.3 %) than viral (7.7 %). At 90 days, 68.4 % reached a good outcome (mRS $\leq$ 2), and the rate jumped to 75 % among those managed through the integrated pathway. Still, numbers only hint at the story the earlier the match between imaging and PCR, the better the brain survived.

3.15 Pathogen Level Diagnostic Performance

Pathogen-specific analysis (*Supplementary Table S2*) demonstrated the highest MRI–PCR concordance for HSV-1/2 (90.5%) and *Streptococcus pneumoniae* (92.8%), both showing characteristic imaging patterns. MRI sensitivity was lower for enterovirus (57.1%) and EBV (66.6%), where findings were subtle or nonspecific and emphasizing PCR's confirmatory role. Integrated interpretation improved reliability across all pathogens preventing HHV-6 over-diagnosis and supporting earlier HSV-directed therapy.

3.16 Inter Reader Reliability

Inter-reader agreement between the two blinded neuroradiologists was excellent for all imaging parameters ($\kappa = 0.82$, 95 % CI 0.76–0.88; ICC = 0.87, 95 % CI 0.80–0.92), confirming high consistency of MRI feature interpretation.

4- DISCUSSION

Diagnosing encephalitis has always felt like chasing two moving targets at once speed and certainty. Imaging can whisper the truth early, but it sometimes lies. Microbiology, on the other hand, brings proof, yet often too late to matter. This study sat between those worlds and tried to make them talk to each other. By combining advanced MRI with CSF PCR, diagnostic accuracy reached 95% (AUC = 0.96). Not a marginal gain a shift. It means the difference between guessing and knowing [1, 2, 3].

4.1 MRI Alone its brilliance and blind spots

MRI did what it does best: reveal structure, metabolism, perfusion the visible face of infection. Its performance stood solid (AUC = 0.87), echoing earlier studies [4, 5, 6, 7]. Temporal lobe FLAIR brightening, micro-hemorrhage on SWI restricted diffusion the usual suspects of HSV. Bacterial cases drew a different pattern:

Low ADC, lactate peaks. But here's where we pushed further. We turned those impressions into measurable thresholds: FLAIR ratio > 1.4, ADC $< 0.8 \times 10^{-3}$ mm²/s, lactate/Cr > 0.25. Numbers, not adjectives; still, MRI missed its mark sometimes viral cases with no limbic flare, bacterial lesions that faked inflammation. It's powerful, but it doesn't always tell the full biological story [8, 9, 10].

4.2 PCR Alone precise, but fragile

PCR came with better accuracy (AUC = 0.90), but its own cracks showed quickly. Seven patients had every textbook sign of HSV, yet PCR was blank classic early-sampling false negatives [11, 12]. Three others lit up positive for HHV-6 with no matching lesions, a reminder of how chromosomal integration can trick the machine [13]. So, PCR cuts deep, but not always clean. On its own, it can delay therapy or start the wrong one.

4.3 Integration closing the loop

When MRI and PCR finally spoke the same language, accuracy climbed to 0.96. The numbers mattered DeLong $p = 0.01$ vs MRI, $p = 0.04$ vs PCR but what mattered more was the balance it restored. MRI rescued PCR-negative HSV; PCR reined in over-interpreted scans. Each corrected the other's illusion. Past studies kept these fields in separate lanes [14–16]. Here they collided, and from that collision come clarity.

4.4 Pathogen specific resolution

Earlier work often treated encephalitis as one blurred diagnosis [17, 18, 19]. We didn't. MRI shone in HSV (90.5%) and *S. pneumoniae* (92.8%), but dimmed for enterovirus and EBV. That nuance matters HSV-like imaging justifies immediate antivirals even before PCR, while subtle patterns still demand molecular proof. Integration turns statistics into bedside instinct.

4.5 Quantitative biomarkers turning light into data

The real innovation, Numbers that behave like biomarkers:

- ADC $< 0.8 \times 10^{-3}$ mm²/s → bacterial;
- FLAIR > 1.4 → viral (especially HSV);
- lactate/Cr > 0.25 → bacterial metabolism;
- ASL-CBF > 70 ml/100 g/min → viral hyperperfusion.

These aren't decorative metrics they're diagnostic handles. Inter-reader agreement was high ($\kappa = 0.82$; ICC = 0.87). No earlier work truly linked such quantification with PCR-confirmed infection [20, 21]. This study bridged radiology's visuals with microbiology's code.

4.6 Bacterial virulence and the culture echo

Culture still speaks the old language of proof. It was positive in 62.8% of bacterial cases mainly *S. pneumoniae* and *L. monocytogenes* mirroring global trends [22, 23]. These patients had high neutrophils, high protein, low glucose, and the cold precision of low ADC. The 37% who were culture-negative was momstly postantibiotic-ghosts. There MRI + PCR revived the truth, compensating for culture's fading sensitivity [24]. Together they map infection across biology, chemistry, and anatomy a rare triangulation in the literature.

4.7 Decision curve and clinical reality

Numbers alone don't heal anyone. Decision-Curve Analysis showed what counts: net benefit. Across thresholds from 10–80%, the integrated model saved time (therapy in 10 h vs 24 h) and lives (mRS ≤ 2 in 75%). It met the promise of antimicrobial stewardship precision without waste [25]. Integration didn't just sharpen diagnosis; it accelerated recovery.

4.8 Limitations and the next horizon

Yes, it's one center, 76 patients, few EBV or HHV-6. Expert panels can bias; ASL and MRS aren't everywhere. But those limits aren't failures they're starting points. Scaling this work across centers, automating feature extraction, and using AI radiomics could make these biomarkers part of daily diagnostic language.

4.9 Clinical implications and the road forward

Three takeaways stand firm:

1. Diagnosis must adapt to the pathogen one rule doesn't fit all.
2. Quantitative imaging replaces description with evidence.
3. Integration changes outcome, not just accuracy.

Where others described, we measured. Where they pooled, we separated. Where they stopped at numbers, we showed survival. Integration of MRI and PCR is not a luxury of technology anymore; it's becoming the minimum standard for serious encephalitis care.

5- CONCLUSION

This study demonstrates that no single modality suffices for the reliable diagnosis of encephalitis. MRI revealed structural, metabolic, and perfusion signatures, while CSF PCR delivered pathogen-specific confirmation. Each, when used in isolation, failed patients at critical moments. Yet when integrated, they achieved 95% diagnostic accuracy, a statistically validated superiority confirmed by DeLong testing.

Beyond accuracy, two innovations distinguish this work:

1. Pathogen-level differentiation diagnostic reliability varies across microorganisms, with MRI excelling in *HSV* and *S. pneumoniae*, while PCR remains essential for enterovirus and *EBV*.

2. Quantitative imaging biomarkers subjective descriptors replaced by measurable thresholds (ADC, FLAIR, MRS, ASL) that align radiologic patterns with microbiological confirmation.

Integration thus emerges not as a luxury but as a clinical safeguard one that prevents both overtreatment and diagnostic delay. By demonstrating improved accuracy, shorter time-to-therapy, and better functional outcomes, this study supports the adoption of combined MRI–PCR interpretation as the new diagnostic standard of care for encephalitis.

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