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Original Article

Diagnostic Accuracy of Contrast-Enhanced FLAIR MRI in the Diagnosis of Meningitis, Keeping CSF Analysis as the Gold Standard

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ABSTRACT

Meningitis is a potentially life-threatening inflammation of the meninges that requires prompt diagnosis to reduce neurological complications and mortality. Cerebrospinal fluid (CSF) analysis remains the reference standard, but contrast-enhanced fluid-attenuated inversion recovery magnetic resonance imaging (CE-FLAIR MRI) may improve detection of meningeal enhancement and complement CSF assessment. **Objective:** To determine the diagnostic accuracy of CE-FLAIR MRI for meningitis using CSF analysis as the reference standard. **Methods:** This cross-sectional diagnostic accuracy study included 103 patients with suspected meningitis at MTI/Hayatabad Medical Complex, Peshawar, from May to November 2022. All participants underwent CE-FLAIR MRI and CSF analysis. Diagnostic performance was assessed using a 2 × 2 contingency table, and sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall accuracy were calculated with 95% confidence intervals. **Results:** Among 103 patients, 61 were CSF-positive, and 42 were CSF-negative. CE-FLAIR MRI identified 55 true-positive, 34 true-negative, 8 false-positive, and 6 false-negative cases. Sensitivity was 90.2% (95% CI: 80.2–95.4), specificity 81.0% (66.7–90.0), PPV 87.3% (76.9–93.4), NPV 85.0% (70.9–92.9), and overall accuracy 86.4% (78.5–91.7). CE-FLAIR MRI showed a strong association with CSF-confirmed meningitis (Cramer's V = 0.717, p<0.001). **Conclusions:** CE-FLAIR MRI showed good diagnostic performance and may serve as a useful non-invasive adjunct to CSF analysis in suspected meningitis; however, it should not replace CSF assessment where lumbar puncture is feasible.

INTRODUCTION

Meningitis is an acute or subacute inflammation of the meninges and cerebrospinal fluid (CSF) spaces caused by bacterial, viral, tuberculous, fungal, or other infectious agents. Delayed diagnosis may result in seizures, hydrocephalus, infarction, cranial nerve dysfunction, cognitive impairment, and death [1]. Clinical features such as fever, headache, vomiting, neck stiffness, altered consciousness, and seizures may raise suspicion but are not sufficiently specific for definitive diagnosis; therefore, laboratory and imaging evaluation remains essential [2]. Lumbar puncture with CSF analysis remains the reference standard for suspected meningitis. Evaluation commonly includes leukocyte count and differential, protein, glucose, CSF-to-serum glucose ratio, Gram stain, culture, and other microbiological or molecular tests. However, CSF assessment may be delayed or contraindicated in patients with raised intracranial pressure, severe clinical instability, coagulation disorders, or focal neurological deficits, and microbiological yield may be reduced after prior antimicrobial therapy [3, 4]. These limitations support the use of imaging as a complementary diagnostic tool. Magnetic resonance imaging (MRI) is more sensitive than computed tomography for detecting meningeal inflammation and related intracranial complications. Contrast-enhanced FLAIR suppresses the normal CSF signal and improves visualization of abnormal gadolinium

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accumulation within the subarachnoid spaces, making subtle leptomeningeal, sulcal, and basal cisternal enhancement easier to detect than on some conventional post-contrast sequences [5]. Recent studies have reported good diagnostic performance of CE-FLAIR MRI in suspected meningitis. Khalid *et al.* reported a sensitivity of 95.08% and specificity of 82.5% for contrast-enhanced T2-FLAIR using CSF analysis as the reference standard [6]. Other studies have similarly shown that post-contrast FLAIR may improve detection of subtle meningeal enhancement. Nevertheless, diagnostic performance varies according to disease etiology, patient characteristics, MRI protocol, disease severity, and image interpretation[3,7].

Few studies have evaluated the correlation of specific CE-FLAIR MRI abnormalities (leptomeningeal, sulcal, basal cisternal, ependymal/ventricular enhancement, and cerebral edema) with CSF proven meningitis in a single well-defined study population. Despite increasing evidence supporting CE-FLAIR MRI, local data on its diagnostic performance against CSF analysis remain limited. Therefore, this study aimed to determine the diagnostic accuracy of CE-FLAIR MRI for meningitis using CSF analysis as the reference standard and to evaluate the association of specific MRI findings with CSF-confirmed disease.

METHODS

A cross-sectional diagnostic accuracy study was conducted at MTI/Hayatabad Medical Complex, Peshawar, over six months, from May 2022 to November 2022, to determine the diagnostic performance of contrast-enhanced fluid-attenuated inversion recovery magnetic resonance imaging (CE-FLAIR MRI) for meningitis, using cerebrospinal fluid (CSF) analysis as the reference standard. Ethical approval was obtained from the Institutional Research and Ethical Board of MTI/Hayatabad Medical Complex, Peshawar (Ref. No. 698/HEC/B&PSC/2022, dated 27 May 2022). Written informed consent was obtained from eligible participants or their legally authorized attendants, and patient confidentiality was maintained throughout the study. Patients of either sex with clinical suspicion of meningitis who underwent both CE-FLAIR MRI and CSF examination were enrolled through non-probability consecutive sampling. Patients were excluded if MRI or CSF results were incomplete, the MRI examination was technically inadequate, MRI or intravenous contrast was contraindicated, CSF examination could not be performed when clinically indicated, or clinical information required for comparison of the index and reference tests was incomplete. A total of 103 patients were included. The sample size was determined for a diagnostic accuracy study at a 95% confidence level using the prevalence-adjusted approach for estimating sensitivity and specificity described by Buderer [8]. Anticipated sensitivity (95.08%) and specificity (82.5%) were obtained from the previously published study by Khalid et al. [6]. The sample-size calculations were based on the expected prevalence of meningitis among clinically suspected patients and the prespecified absolute precision for estimation of diagnostic performance. For sensitivity, the calculation followed $n = Z^2 \times Se(1–Se)/(d^2 \times P)$, whereas for specificity it followed $n = Z^2 \times Sp(1–Sp)/(d^2 \times [1–P])$, where Z represents the standard normal value at 95% confidence, Se sensitivity, Sp specificity, d absolute precision, and P expected disease prevalence. The larger calculated requirement was adopted, giving a final sample size of 103 participants. Consecutive recruitment continued until the required sample was achieved. Demographic and clinical data included age, sex, duration of symptoms, fever, headache, neck stiffness, vomiting, altered consciousness, seizures, body temperature, and Glasgow Coma Scale score. Brain MRI was performed according to the institutional MRI protocol. CE-FLAIR images were evaluated for evidence of meningitis and classified as positive or negative. Recorded imaging features included leptomeningeal enhancement, sulcal enhancement, basal cisternal enhancement, ependymal/ventricular enhancement, and cerebral edema. CSF examination performed after lumbar puncture served as the reference standard. The reference standard was predefined before data collection and was based solely on CSF laboratory parameters, independent of CE-FLAIR MRI findings and clinical suspicion. CSF white blood cell (WBC) count and differential, protein concentration, glucose concentration, gross appearance, Gram stain, and culture were recorded, and the CSF-to-serum glucose ratio was calculated using concurrent serum glucose. The following thresholds were used: pleocytosis, CSF WBC >5 cells/μL; elevated protein, >45 mg/dL; low glucose, <40 mg/dL; and abnormally low CSF-to-serum glucose ratio, ≤0.40. CSF-positive meningitis was defined by at least one of the following prespecified criteria: positive CSF culture for a pathogenic organism; positive Gram stain with a compatible CSF profile; or CSF pleocytosis (>5 WBC/μL) plus at least one abnormal biochemical marker (protein >45 mg/dL, glucose <40 mg/dL, or CSF-to-serum glucose ratio ≤0.40). When culture or Gram stain was positive, the case was classified as CSF-positive even if pleocytosis was absent. Patients who did not meet any of these criteria were classified as CSF-negative. Clinical suspicion alone was not sufficient for a CSF-positive classification; it was used only to define the study population. CSF samples were processed and interpreted by laboratory personnel blinded to CE-FLAIR MRI results, and MRI readers were blinded to CSF results.

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The reference standard was applied uniformly before comparison with MRI. These parameters are consistent with established CSF interpretation standards for suspected meningitis [9]. CE-FLAIR MRI findings were compared with the CSF reference diagnosis and classified as true-positive (MRI positive/CSF positive), false-positive (MRI positive/CSF negative), false-negative (MRI negative/CSF positive), or true-negative (MRI negative/CSF negative). Clinical, radiological, and laboratory procedures were applied consistently throughout the study, and data were checked for completeness and internal consistency before statistical analysis.

IBM SPSS version 26.0 was used for data analysis. Normality of continuous variables was assessed using the Shapiro–Wilk test and graphical inspection. Normally distributed variables were summarized as mean ± SD and compared between CSF-positive and CSF-negative groups using the independent-samples t-test. When Levene's test indicated unequal variances, the unequal-variance form of the test was used. Non-normally distributed variables were expressed as median and interquartile range and compared using the Mann–Whitney U test. Categorical variables were reported as frequencies and percentages and compared using Pearson's chi-square test; Fisher's exact test was used where expected cell counts were small. Cramer's V was used to describe the strength of statistically significant categorical associations. Diagnostic accuracy was assessed using a 2 × 2 contingency table. Sensitivity was calculated as TP/(TP+FN), specificity as TN/(TN+FP), PPV as TP/(TP+FP), NPV as TN/(TN+FN), and overall diagnostic accuracy as (TP+TN)/N. Ninety-five percent confidence intervals for sensitivity, specificity, PPV, NPV, and accuracy were calculated from the corresponding binomial proportions using the Wilson score method and were applied consistently to all diagnostic performance estimates. The association between CE-FLAIR MRI and CSF-confirmed meningitis was evaluated using Pearson's chi-square test and Cramer's V. Clinical, MRI, and CSF variables represented prespecified secondary/exploratory comparisons rather than multiple primary hypotheses; therefore, no formal adjustment for multiple comparisons was applied, and individual p-values were interpreted cautiously. All tests were two-sided, and $p<0.05$ was considered statistically significant.

RESULTS

A total of 103 patients were included in the analysis, of whom 61 were classified as CSF-positive and 42 as CSF-negative for meningitis. Demographic characteristics were generally comparable between the two groups. Among the evaluated clinical features, headache, neck stiffness, and vomiting showed statistically significant associations with CSF-confirmed meningitis, whereas age, sex, fever, altered consciousness, and seizures did not differ significantly between the groups. Symptom duration was also significantly longer among CSF-positive patients (p=0.035) (Table 1).

Table 1: Demographic and Clinical Characteristics According to CSF Diagnosis of Meningitis

Characteristics	CSF-positive (n=61), n (%)	CSF-negative (n=42), n (%)	Test Statistic	χ^2	Cramer's V†	p-value
Age, years (mean ± SD)	36.74 ± 13.17	33.98 ± 13.35	t = −1.040	—	—	0.301
Male	34 (55.7%)	23 (54.8%)	—	0.010	—	0.922
Female	27 (44.3%)	19 (45.2%)	—	—	—	—
Fever, Yes	55 (90.2%)	35 (83.3%)	—	1.052	—	0.305
Headache, Yes	57 (93.4%)	29 (69.0%)	—	10.742	0.323	0.001
Neck Stiffness, Yes	44 (72.1%)	16 (38.1%)	—	11.849	0.339	0.001
Vomiting, Yes	36 (59.0%)	14 (33.3%)	—	6.568	0.253	0.010
Altered Consciousness, Yes	23 (37.7%)	9 (21.4%)	—	3.077	—	0.079
Seizures, Yes	11 (18.0%)	6 (14.3%)	—	0.253	—	0.615
Symptom Duration, Days, Median (IQR)	6.0 (3.50)	5.0 (2.25)	U = 970.50	—	—	0.035

Values are presented as mean ± SD, median (IQR), or n (%), as appropriate. χ^2: Pearson chi-square statistic; U: Mann–Whitney U statistic. † Cramer's V is reported for statistically significant categorical associations. Bold p-values indicate statistical significance at $p<0.05$

CE-FLAIR MRI findings showed clear associations with CSF-confirmed meningitis. Overall CE-FLAIR MRI positivity demonstrated the strongest association with CSF diagnosis (Cramer's V = 0.717, $p<0.001$). Leptomeningeal, sulcal, and basal cisternal enhancement were also significantly associated with CSF-positive disease, while cerebral edema showed a weaker but statistically significant association. In contrast, ependymal/ventricular enhancement was not significantly associated with CSF diagnosis (Table 2).

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Table 2: Contrast-Enhanced FLAIR MRI Findings According to CSF Diagnosis of Meningitis

MRI Finding	CSF-positive (n=61), n (%)	CSF-negative (n=42), n (%)	χ^2	Cramer's V†	p-value
CE-FLAIR MRI Positive	55 (90.2%)	8 (19.0%)	52.961	0.717	<0.001
Leptomeningeal Enhancement	44 (72.1%)	5 (11.9%)	36.174	0.593	<0.001
Sulcal Enhancement	34 (55.7%)	4 (9.5%)	22.817	0.471	<0.001
Basal Cisternal Enhancement	20 (32.8%)	2 (4.8%)	11.631	0.336	0.001
Ependymal/Ventricular Enhancement	12 (19.7%)	4 (9.5%)	1.952	–	0.162
Cerebral Edema	13 (21.3%)	1 (2.4%)	7.590	0.271	0.006

† Cramer's V is shown for statistically significant associations. Bold p-values indicate statistical significance at $p < 0.05$.

CSF laboratory profiles differed substantially between CSF-positive and CSF-negative patients. CSF-positive patients demonstrated higher CSF WBC counts, neutrophil percentages, and protein concentrations, together with lower lymphocyte percentages, CSF glucose concentrations, and CSF-to-serum glucose ratios. Serum glucose did not differ significantly between the groups. Among categorical CSF findings, elevated protein, abnormal CSF appearance, low CSF glucose, Gram-stain positivity, and culture positivity were all significantly associated with CSF-confirmed meningitis (Table 3).

Table 3: CSF Laboratory Findings According to CSF Diagnosis of Meningitis

CSF Parameters	CSF-positive (n=61), n (%) / Mean ± SD	CSF-negative (n=42), n (%) / Mean ± SD	Difference (95% CI)†	Test Statistic	χ^2	Cramer's V†	p-value
CSF WBC, cells/µL, median (IQR)	194.0 (189.5)	8.0 (6.0)	–	U = 0.000	–	–	<0.001
CSF Neutrophils	61.11 ± 19.20	29.10 ± 11.63	32.02 (25.98 to 38.06)	t = –10.519	–	–	<0.001
CSF Lymphocytes	38.89 ± 19.20	70.90 ± 11.63	–32.02 (–38.06 to –25.98)	t = 10.519	–	–	<0.001
CSF Protein, mg/dL	107.59 ± 41.57	42.36 ± 16.30	65.23 (53.52 to 76.93)	t = –11.081	–	–	<0.001
CSF Glucose, mg/dL	38.64 ± 12.61	60.08 ± 13.98	–21.44 (–26.68 to –16.19)	t = 8.109	–	–	<0.001
Serum Glucose, mg/dL	102.84 ± 17.45	100.15 ± 12.71	2.70 (–3.55 to 8.94)	t = –0.856	–	–	0.394
CSF/Serum Glucose Ratio, Median (IQR)	0.39 (0.20)	0.61 (0.22)	–	U = 387.000	–	–	<0.001
CSF Appearance	–	–	–	–	32.868	0.565	<0.001
Clear	19 (31.1%)	36 (85.7%)	–	–	–	–	–
Slightly Turbid	18 (29.5%)	6 (14.3%)	–	–	–	–	–
Turbid	24 (39.3%)	0 (0.0%)	–	–	–	–	–
Gram Stain Positive	21 (34.4%)	0 (0.0%)	–	–	18.162	0.420	<0.001
CSF Culture Positive	13 (21.3%)	0 (0.0%)	–	–	10.244	0.315	0.001
Elevated CSF Protein	61 (100.0%)	18 (42.9%)	–	–	45.447	0.664	<0.001
Low CSF Glucose	31 (50.8%)	2 (4.8%)	–	–	24.233	0.485	<0.001

† Difference is presented as CSF-positive minus CSF-negative, with 95% CI. The confidence intervals were derived directly from the independent-samples t-test output; signs were reversed where necessary because SPSS originally calculated the difference as CSF-negative minus CSF-positive. ‡ Cramer's V is presented for statistically significant categorical associations

Comparison of CE-FLAIR MRI with the CSF reference standard identified 55 true-positive, 34 true-negative, 8 false-positive, and 6 false-negative cases. CE-FLAIR MRI findings showed a statistically significant and strong association with CSF-confirmed meningitis (Pearson χ^2 = 52.961, Cramer's V = 0.717, p<0.001)(Table 4).

Table 4: Diagnostic Accuracy of Contrast-Enhanced FLAIR MRI for Meningitis Using CSF Analysis as the Gold Standard

CE-FLAIR MRI	CSF Positive	CSF Negative	Total
Positive	55 (TP)	8 (FP)	63
Negative	6 (FN)	34 (TN)	40
Total	61	42	103

Pearson χ^2 = 52.961; Cramer's V = 0.717; p<0.001

Diagnostic performance estimates derived from the 2×2 comparison are summarized. CE-FLAIR MRI demonstrated high sensitivity with good specificity, predictive values, and overall diagnostic accuracy when CSF analysis was used as the reference standard (Table 5).

Table 5: Diagnostic Accuracy Parameters of Contrast-Enhanced FLAIR MRI

Diagnostic Parameters	Value	95% CI*
Sensitivity	90.2%	80.2–95.4
Specificity	81.0%	66.7–90.0
Positive Predictive Value (PPV)	87.3%	76.9–93.4
Negative Predictive Value (NPV)	85.0%	70.9–92.9
Overall diagnostic accuracy	86.4%	78.5–91.7

*95% confidence intervals were calculated using the Wilson method

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DISCUSSION

The present study showed that CE-FLAIR MRI had good diagnostic performance for meningitis when CSF analysis was used as the reference standard, with a sensitivity of 90.2%, specificity of 81.0%, PPV of 87.3%, NPV of 85.0%, and overall accuracy of 86.4%. These findings are broadly comparable with Khalid *et al.* who reported sensitivity of 95.08%, specificity of 82.5%, and accuracy of 90.1% for contrast-enhanced T2-FLAIR [6]. Similar diagnostic performance has also been reported by Sanjay *et al.* and Mushtaq *et al.* [10, 11]. The modestly lower specificity and accuracy observed in the present study may reflect differences in case selection, disease spectrum, stage of infection, MRI interpretation, and underlying meningitis etiology. Among the imaging findings, leptomeningeal and sulcal enhancement showed particularly important associations with CSF-confirmed meningitis, while basal cisternal enhancement and cerebral edema were also significantly associated with disease. Ependymal/ventricular enhancement was comparatively less discriminatory. These findings are consistent with Mishra *et al.* who demonstrated high sensitivity of post-contrast FLAIR for meningeal and sulcal abnormalities compared with other post-contrast MRI sequences [12]. Previous evidence also supports the biological basis of CE-FLAIR enhancement through disruption of the blood-CSF and blood-brain barriers, allowing greater visualization of abnormal gadolinium accumulation [13, 14]. Radiomics-based evaluation has further suggested that subtle basal cisternal abnormalities may be identified even when conventional MRI changes are limited [15]. The CSF findings supported the imaging results. CSF-positive patients showed higher WBC counts, neutrophil proportions, and protein concentrations, together with lower glucose levels and CSF-to-serum glucose ratios. Elevated protein, abnormal CSF appearance, low glucose, Gram-stain positivity, and culture positivity were also significantly associated with confirmed meningitis. Goto *et al.* similarly reported associations between abnormal CSF parameters and MRI enhancement in bacterial and tuberculous meningitis [16]. Other studies have continued to demonstrate the importance of CSF cellular, biochemical, and microbiological assessment even with the increasing availability of molecular diagnostic methods [17-19]. These findings reinforce the complementary roles of imaging and CSF analysis rather than supporting replacement of the reference-standard investigation by MRI alone. Clinical features also showed variable diagnostic value. Headache, neck stiffness, vomiting, and longer symptom duration were associated with CSF-confirmed meningitis, whereas age, sex, fever, altered consciousness, and seizures were not significantly different between the groups. This variability indicates that individual clinical features may have limited discriminatory ability when patients present with heterogeneous forms of meningitis. Previous studies of tuberculous meningitis have similarly demonstrated considerable variation in clinical manifestations and MRI abnormalities [20, 21]. In pediatric patients, Shabbir and Sheikh also reported a high PPV for CE-FLAIR MRI when CSF analysis was used as the reference standard [22]. Taken together, these findings indicate that CE-FLAIR MRI is a useful adjunctive imaging technique for suspected meningitis, particularly for detecting subtle meningeal enhancement. Its sensitivity of 90.2% supports its value in identifying patients with meningeal disease; however, positive enhancement is not specific to a single infectious etiology, and MRI findings should therefore be interpreted together with clinical and CSF findings. Comparative evidence similarly suggests that CE-FLAIR may provide greater sensitivity for subtle meningeal enhancement than conventional contrast-enhanced T1-weighted imaging while remaining complementary to other MRI sequences [12].

This study has several limitations. It was conducted at a single center with a relatively small sample, and different etiological types of meningitis were not analyzed separately. MRI interpretation may also have been influenced by disease stage and observer experience, while interobserver agreement and direct comparison with newer three-dimensional post-contrast sequences were not assessed. Future multicenter prospective studies should evaluate CE-FLAIR separately in bacterial, viral, fungal, and tuberculous meningitis, assess inter-reader reproducibility, and directly compare CE-FLAIR with advanced 3D post-contrast techniques. Quantitative and radiomics-based approaches may also be explored to determine whether they can further improve diagnostic performance.

CONCLUSIONS

CE-FLAIR MRI demonstrated good diagnostic performance for meningitis, with high sensitivity and acceptable specificity when CSF analysis was used as the reference standard. Leptomeningeal, sulcal, and basal cisternal enhancement were the most relevant imaging findings associated with CSF-confirmed disease. CE-FLAIR MRI may therefore serve as a useful non-invasive adjunct in patients with suspected meningitis, but it should be interpreted alongside clinical findings and CSF analysis rather than used as a replacement for the reference-standard evaluation.

Authors' Contribution

Conceptualization: AS
Methodology: FM
Formal analysis: NM, SI
Writing and Drafting: AS, FM, MK, AW, NM, SI
Review and Editing: AS, FM, MK, AW, NM, SI

All authors approved the final manuscript and take responsibility for the integrity of the work

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Conflict of Interest

All the authors declare no conflict of interest.

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