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# Diagnostic Accuracy of Postcontrast FLAIR MRI with Subtraction for Detecting Leptomeningeal Disease

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**ABSTRACT**

In this study, we aimed to determine the accuracy of post-contrast FLAIR imaging with subtraction for detecting leptomeningeal disease. We retrospectively examined 58 patients who underwent post-contrast FLAIR imaging with subtraction sequences for leptomeningeal enhancement. The analysis consisted of leptomeningeal enhancement interpretation on pre- and post-Gd 2D-FLAIR coregistered images with subtraction (technique A, the reference standard), 2D-FLAIR post-contrast images (technique B) and 3D-T1WI post-contrast images (technique C). The diagnoses were confirmed by CSF cytology and final clinical diagnosis. Diagnostic tests and κ agreement were used to compare between each study. Leptomeningeal contrast enhancement appreciated on techniques A, B and C for 9 patients (15.5%, $P < 0.001$), 8 patients (13.8%, $P < 0.001$) and 3 patients (5.2%, $P = 0.003$), respectively. Using technique A as the reference standard, both techniques B and C had similar specificity (100%) and PPV (100%). While the sensitivity and NPV of techniques B and C were 88.9% vs 33.3% ($P < 0.001$) and 98% vs 89.1% ($P = 0.003$), respectively. Technique A had the highest reproducibility among all techniques (κ agreement, $P < 0.001$). Pre- and post-contrast 2D-FLAIR coregistered images with subtraction had higher sensitivity, NPV and diagnostic accuracy compared to 2D-FLAIR post-contrast images and 3D-T1WI post-contrast images in the diagnosis of diseases involving leptomeninges.

**Keywords:** MRI; FLAIR; Subtraction; Leptomeningeal disease

## 1. Introduction

Magnetic resonance imaging (MRI) techniques and imaging sequences are crucial for the detection and diagnosis of meningeal and parenchymal lesions [1, 2].

There have been some previous studies demonstrating the utility of post-

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contrast T2 FLAIR in the evaluation of intracranial enhancement [3, 4]. Post-contrast FLAIR sequence enhanced sensitivity and specificity performs better in the diagnosis of meningitis as compared to post-contrast T1W sequencing [5]. Delayed post-contrast T2 FLAIR images were also better than T1 MTC images in the diagnosis of infectious meningitis and leptomeningeal metastasis [6]. In cases with multiple sclerosis, images with subtraction enhanced accuracy for the detection of leptomeningeal enhancement had a diminished false-positive rate and lower interpretation time [7].

However, there are only a few studies on the utility of post-contrast FLAIR imaging with subtraction in detecting leptomeningeal diseases [7, 8]. Furthermore, there have been no studies evaluating the accuracy and reproducibility of post-contrast FLAIR imaging with subtraction of leptomeningeal enhancement in many leptomeningeal diseases.

Therefore, the purpose of this study was to determine the accuracy of post-contrast FLAIR imaging with subtraction for detecting leptomeningeal disease.

## 2. Materials and Methods

### 2.1 Study population

This study was approved by the Human Ethics Committee of our institution (Faculty of Medicine, Thammasat University).

The medical data of patients who underwent postcontrast 2D FLAIR imaging with subtraction at Thammasat University Hospital, Thailand, from Jan 2019 to Dec 2020 were retrospectively collected.

The inclusion criteria were the following: 1) 18 years old and above; 2) Patients who underwent postcontrast 2D FLAIR imaging with subtraction sequences. Exclusion criteria were the following: 1) Imaging results contained severe artifacts which degraded image quality; 2) Patients with intracranial or intraorbital metallic objects, or magnetically/electrically activated implants; 4) Patient was pregnant; 5) Patient was under general anesthesia.

Fifty-eight patients were enrolled in our study. Patient demographics were collected from the medical records.

### 2.2 Imaging Techniques

All patients were investigated by a 3 Tesla scanner (Siemens Magnetom Skyra) or a 1.5 Tesla scanner (Siemens Magnetom Aera).

The existence of leptomeningeal enhancement was evaluated using 2D-FLAIR imaging and spin-echo 3D-T1WI sequences in pre- and post-contrast images. The image acquisition for 2D-FLAIR was as followed; TR/TI/TE = 11000/2690/98 ms, matrix = 384 x 218, voxel size = 0.6x0.6x5.0 $mm^3$, right to left frequency direction. The post-contrast 2D-FLAIR sequence was immediately performed after the pre-contrast 2D FLAIR was obtained. Gadolinium injection was administered with the dose level of 0.1 mmol/kg. This sequence was 3 minutes long.

The image acquisition for spin-echo 3D T1WI was as follows: 203 x 384 matrix and 220 x 180 $mm^2$ FOV, resulting in a nominal in-plane resolution of 0.6x0.6x1.5 $mm^3$, 1.5-mm slice thickness without gap, TE/TR = 11/588 ms. The post-contrast 3D-T1WI sequence was acquired after post-contrast 2D FLAIR in every case. This sequence was 2 minutes long.

The 2D-FLAIR post-contrast images with subtraction were acquired by coregistration and voxel-wise subtraction between pre- and post-contrast 2D-FLAIR images using Syngovia workstation software, version VB30.

### 2.3 MRI assessment

Leptomeningeal contrast enhancement analysis was evaluated independently by two radiologists. They were totally unaware of the imaging sequences for each patient. The images were assessed firstly by pre- and post-contrast 2D-FLAIR coregistered with

subtraction (technique A), secondly by postcontrast 2D-FLAIR images (technique B) and lastly by postcontrast 3D-T1WI images (technique C). The image interpretation for each sequence was randomized to avoid potential interpretation bias. A 2-week delay was required for all 3 techniques to diminish recall bias.

The nasal mucosa, pituitary stalk, choroid plexus, cavernous sinus, cortical venous enhancement and pineal enhancement were concluded as normal on contrast-enhanced FLAIR images with subtraction [8].

A low-level hyperintensity presented on the subtracted images which, when found completely along the sulcal contour and not vessels, is termed "pseudo-enhancement" [7].

Positive contrast enhancement in technique A, which excludes normal enhancement areas and pseudo-enhancement, was defined as meeting at least 1 of the following 3 criteria: 1) Lesion conspicuity; 2) Lesion extension or; 3) Increased degree of contrast enhancement. Positive contrast enhancement on technique B, which excludes normal enhancement area and pseudo-enhancement used this same definition. Technique C, which excludes normal enhancement areas and hyperintense on T1W image, used this definition as well.

Patients were categorized as presence or absence of leptomeningeal disease based on CSF cytology and final clinical diagnosis. Infectious leptomeningitis was diagnosed if the presence of an abnormal CSF profile was acquired within 48 hours before or after MRI. Leptomeningeal metastasis was diagnosed if the presence of an abnormal CSF profile was obtained either 14 days before or after MRI. Absence of leptomeningeal disease was established if there was no clinical confirmation of leptomeningeal disease within the 2-month follow-up period and no positive CSF examination results were found.

Analysis of reproducibility for detecting leptomeningeal enhancement interpreted by two reviewers was performed in all patients, using the same approach.

Consensus was used to resolve any discordance between the conclusions of the two reviewers.

### 2.4 Statistical analyses

SPSS version 23.0 (IBM) was used for statistical analysis.

Sensitivity, specificity, negative predictive value and positive predictive value were calculated for all techniques, using CSF analysis results or final clinical diagnosis as the gold standard.

The ability to discriminate between all 3 techniques was determined by using the area under the receiver operating characteristic curve (ROC area) [9].

Interobserver reliability was analyzed by using the kappa statistic, with a kappa value of 0.648 suggestive of substantial agreement.

## 3. Results

### 3.1 Demographics

Nine of 58 patients showed leptomeningeal disease; of these 9, 5 patients were female, and 4 patients were male. The mean age at diagnosis was 49.78 ±15.56 years (range 27-67 years). Eight patients were positive for malignancy, 1 patient was SLE (aseptic meningitis). Detailed patient demographics are summarized in Table 1.

**Table 1.** Patient demographics.

| Variables | Total | | Leptomeningeal disease | | | |
|---|---|---|---|---|---|---|
| | | | Yes | | No | |
| | n | % | n | % | n | % |
| **Gender** | | | | | | |
| Male | 24 | 41.4 | 4 | 16.7 | 20 | 83.3 |
| Female | 34 | 58.6 | 5 | 14.7 | 29 | 85.3 |
| **Age** | | | | | | |
| Mean±SD | 57.86±14.26 | | 49.78±15.56 | | 52.24±14.14 | |
| (Min-Max) | (19-79) | | (27-67) | | (19-79) | |
| **Malignancy** | | | | | | |
| Yes | 8 | 13.8 | 8 | 100 | - | - |
| No | 50 | 86.2 | 1 | 2 | 49 | 98 |
| **Total** | 58 | 100 | 9 | 15.5 | 49 | 84.5 |

### 3.2 Leptomeningeal enhancement among 3 MRI techniques

There were 9 (15.5%) patients with positive leptomeningeal contrast enhancement demonstrated on technique A ($P < 0.001$); 8 (13.8%) on technique B ($P < 0.001$); and 3 (5.2%) on technique C ($P = 0.003$).

Fig. 1 shows leptomeningeal enhancement areas using subtraction images, regarding evaluation of techniques A, B and C.

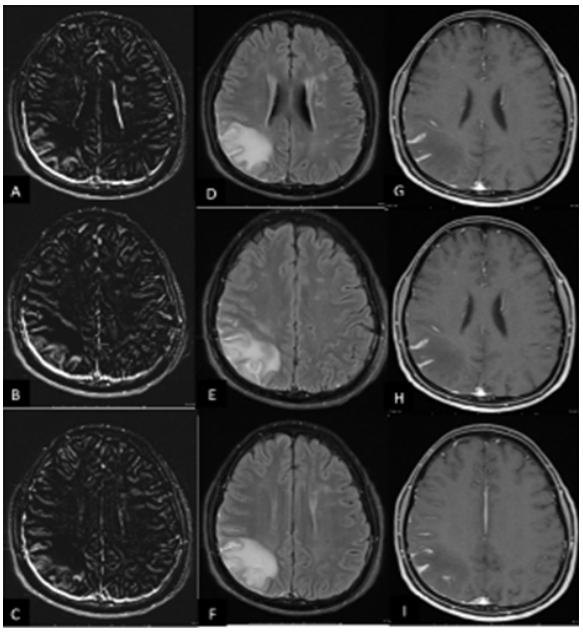


**Fig. 1.** Leptomeningeal enhancement detection using image subtraction A–C, Coregistered pre- /post-contrast 2D-FLAIR subtracted images in the axial plane**.** D–F, Post-contrast 2D-FLAIR images in the axial plane**.** G–I, Post-contrast 3D-T1WI images in the axial plane. Owing to the assistance of pre- and post-contrast 2D-FLAIR subtraction images, it was easier to spot a true leptomeningeal contrast enhancement at the right parietal lobe, seen above.

### 3.3 Sensitivity, Specificity, and Positive and Negative Predictive Values in all Techniques

Overall, technique A had 100% sensitivity, 100% specificity, 100% PPV and 100% NPV($P$< 0.001); technique B had 88.9 % sensitivity, 100% specificity, 100% PPV and 98% NPV ($P$ < 0.001); technique C had 33.3% sensitivity, 100% specificity, 100% PPV and 89.1% NPV($P$< 0.001) (Table 2). For technique A, the area under the curve (AUC) remained at 1.0; for technique B, the AUC increased from 0.67 to 0.94 (Fig. 2).

### 3.4 Reproducibility of Leptomeningeal Contrast-Enhancement Assessment Using the 3 Techniques

The Cohen $\kappa$ agreement for the presence of leptomeningeal contrast enhancement area (presence/absence) was 1.0 *(*$P$ < 0.001) for technique A, 0.92 ($P$ < 0.001) for technique B and 1.0 ($P$ < 0.001) for technique C (Table 3).

**Table 2.** Sensitivity, specificity, positive and negative predictive values of each imaging technique using CSF analysis or final clinical diagnosis as the reference.

| Method | Total | Leptomeningeal disease | | p-value | Sensitivity% | Specificity% | PPV% | NPV% |
|---|---|---|---|---|---|---|---|---|
| | | Yes | No | | | | | |
| **A** | | | | | | | | |
| Positive | 9 | 9 | 0 | <0.001* | 100 | 100 | 100 | 100 |
| Negative | 49 | 0 | 49 | | | | | |
| **B** | | | | | | | | |
| Positive | 8 | 8 | 0 | <0.001* | 88.9 | 100 | 100 | 98 |
| Negative | 50 | 1 | 49 | | | | | |
| **C** | | | | | | | | |
| Positive | 3 | 3 | 0 | 0.003* | 33.3 | 100 | 100 | 89.1 |
| Negative | 55 | 6 | 49 | | | | | |

*Statistical significance at p-value <0.05 determined by Fisher's Exact test. Technique A assessment was performed by using coregistered pre-/ post-contrast 2D-FLAIR subtracted images; technique B, using post-contrast 2D-FLAIR images; and technique C, using post-contrast 3D-T1WI images, PPV; Positive Predictive Value, NPV; Negative Predictive Value.

**Table 3.** The Cohen K agreement for the presence of primary outcome between the two reviewers.

| Technique | Interpretation | Total | Reviewer 1 | | Cohen's kappa coefficient (k) | p-value |
|---|---|---|---|---|---|---|
| | | | Positive | Negative | | |
| **A** | **Reviewer 2** | | | | | |
| | Positive | 9 | 9 | 0 | 1 | <0.001* |
| | Negative | 49 | 0 | 49 | | |
| **B** | **Reviewer 2** | | | | | |
| | Positive | 7 | 8 | 0 | 0.923 | <0.001* |
| | Negative | 51 | 1 | 50 | | |
| **C** | **Reviewer 2** | | | | | |
| | Positive | 3 | 3 | 0 | 1 | <0.001* |
| | Negative | 55 | 0 | 55 | | |

*Statistical significance at p-value <0.05 determined by Fisher's Exact test. Technique A assessment was performed by using coregistered pre-/ post-contrast 2D-FLAIR subtracted images; technique B, using post-contrast 2D-FLAIR images; and technique C, using post-contrast 3D-T1WI images, PPV; Positive Predictive Value, NPV; Negative Predictive Value.

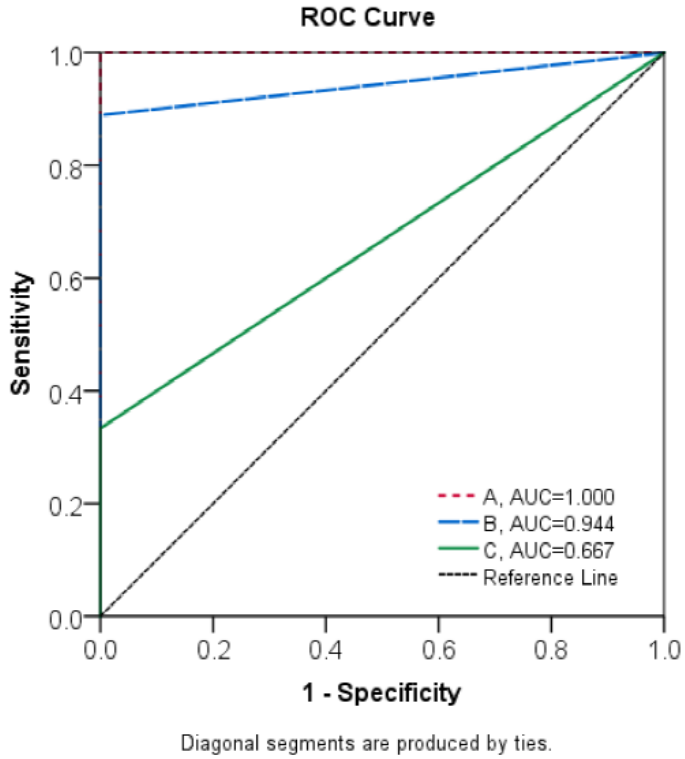


**Fig. 2.** Leptomeningeal enhancement detection using subtraction images A-C, Coregistered pre-/ post-contrast 2D-FLAIR subtracted images in the axial plane**.** D-F, Post-contrast 2D-FLAIR images in the axial plane**.** G–I, Post-contrast 3D-T1WI images in the axial plane. Owing to the assistance of pre- and post-contrast 2D-FLAIR subtraction images, it was easier to spot a true leptomeningeal contrast enhancement at the right parietal lobe.

## 4. Discussion

The role of imaging sequences is crucial for the diagnosis meningeal and parenchymal lesions [1, 2]. In diagnosis of meningitis, conventional sequences such as postcontrast T1-weighted images and

contrast-enhanced FLAIR images have been commonly used. However, contrast-enhanced FLAIR sequences have been reported to be more sensitive and specific than contrast-enhanced T1W sequences for this condition [5]. Subtraction imaging has also been used in patients with multiple sclerosis, which could increase the accuracy of leptomeningeal enhancement area detection, avoid false-positives and decrease reading time [7].

However, there have been a few studies conducted to ascertain the usefulness of post-contrast FLAIR imaging with image subtraction in detecting leptomeningeal disease, though there have been no studies evaluating the accuracy and reproducibility of post-contrast FLAIR imaging with image subtraction for leptomeningeal enhancement in many leptomeningeal diseases. Therefore, the diagnostic accuracy of post-contrast FLAIR imaging with image subtraction for detecting leptomeningeal disease is substantial.

This study shows that technique A has similar specificity and PPV but higher sensitivity and NPV compared to techniques B and C, which is consistent with findings by Zivadinov et al. [7]. Furthermore, by using the AUC as an index, it shows that technique A has higher diagnostic accuracy compared to techniques B and C.

The subtraction approach was particularly useful for decreasing the rates of false-positive and false-negative results for leptomeningeal enhancement, due to the ability to eliminate partial volume of brain parenchyma and blood vessels. This includes removal of unwanted flow artifacts on FLAIR images, particularly at the basal and prepontine cisterns which could masquerade leptomeningeal enhancement in tuberculous meningitis [7, 8].

Most importantly, this study found that the subtraction technique could be a useful tool with high accuracy for fast screening of leptomeningeal contrast enhancement in patients with suspected leptomeningeal disease.

Furthermore, technique A had better sensitivity than technique B (100% vs. 88.9 %, respectively). We suggest that if subtraction is used, data interpretation should be done with this in mind.

In our study, the agreement for the positive leptomeningeal enhancement areas was higher in technique A than it was in technique B.

Post-contrast FLAIR sequencing is not considered as a routine protocol, hence, resident staff might not be proficient in interpreting the results. Our findings suggest that residents using the subtraction technique will have improved diagnostic performance with results comparable to that of a neuroradiologist's.

Additionally, the subtraction approach has a slightly shorter time for detection of leptomeningeal contrast enhancement foci, with an average slightly above 2 minutes used per examination, including source image inspection. With the subtraction approach alone, patients without leptomeningeal contrast enhancement foci could be detected in <1 minute. We believe this is a decent amount of time to add to the reading burden of expert neuroradiologists with high reproducibility among the raters.

### 4.1 Limitations

First, there was small number of the enrolled patients, so statistical power was reduced. In the future, a larger sample size is suggested to enhance the power of the study.

Second, the subtraction technique seems to be susceptible to CSF pulsation or mild patient motion. In this study the postcontrast T1WI was performed prior to FLAIR, and it appeared to improve in the later examinations in which the FLAIR sequence was performed as the last pre-contrast and the first post-contrast sequence [7, 10]. This limitation could be diminished by using the recently developed adaptive motion autocorrection algorithm [11] or new techniques such as PROPELLER (periodically rotated overlapping parallel lines with enhanced reconstruction) [12, 13]. The post-contrast 3D FLAIR technique is also a way to reduce the susceptibility to CSF pulsation, trading off more acquisition time.

Third, comparison between 2D and 3D images for image quality (2D FLAIR vs 3D T1WI) was a limitation in this study, as this was a retrospective study with limited imaging sequences. Further study between post-contrast 3D FLAIR vs 3D T1WI would be helpful to resolve this issue.

## 5. Conclusion

Pre- and post-contrast 2D-FLAIR coregistered with subtracted images had higher sensitivity, NPV and diagnostic accuracy compared to 2D-FLAIR post-contrast images and 3D-T1WI post-contrast images in the diagnosis of leptomeningeal disease.

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