

# Is Lateral Ventricle Apparent Diffusion Coefficient Value Useful in the Diagnosis of Leptomeningeal Carcinomatosis?

## Lateral Ventrikül Görünür Difüzyon Katsayısı Leptomeningeal Karsinomatozis Tanısında Yararlı Olabilir mi?

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**Abstract:** Leptomeningeal carcinomatosis (LMC) is caused by the spread of malignant cells within cerebrospinal fluid (CSF). Diffusion-weighted imaging (DWI) is quantified by the apparent diffusion coefficient (ADC) value. The decreased ADC of CSF in pyogenic ventriculitis due to pleocytosis and the protein content has been reported. With similar argument, we hypothesized ADC in LMC can be decreased due to higher CSF viscosity caused by levated factors such as cell count, total protein. The purpose of our study was to evaluate whether increased CSF viscosity in LMC causes low ADC values in CSF. Thirty-one patients with LMC and 31 age and sex-matched subjects having normal brain MRI were included in this study. ADC measurements were made on both sides in posterior lateral ventricle (LV) and lateral pterigoid muscle (LPM). The ADC ratio (=ADCCSF/ADCLPM) was calculated by dividing the ADC values to prevent individual and device-dependent differences. ADCCSF and ADC ratios were compared between the groups. Both the ADCCSF and ADCCSF/ADCLPM ratio in the LMC group was lower than those in the control group with statistical significance. ROC analysis showed a cutoff value of 2844 for the ADCCSF (sensitivity 51.61%, specificity 96.77%, under curve 0.800) and a cutoff value of 1.97 for the ADC ratio (sensitivity 74.19%, specificity 93.55%, under curve 0.833) for differentiating LMC and control groups. ADC value may be used as a complementary tool to increase diagnostic accuracy of LMC.

**Keywords:** Leptomeningeal carcinomatosis, magnetic resonance imaging, diffusion weighted imaging, ADC value, cerebrospinal fluid, viscosity

**Özet:** Leptomeningeal karsinomatozis (LMK), malign hücrelerin beyin-omurilik sıvısı içinde yayılımından kaynaklanır. Difüzyon ağırlıklı görüntüleme görünür difüzyon katsayısı (GDK) ile kantifiye edilir. Piyojenik ventrikülitte pleositozdan ve protein içeriğinden dolayı düşük GDK değerleri raporlanmıştır. Benzer argümanla, artmış hücre sayısı, total protein gibi faktörlere bağlı artmış viskozite, LMK'de GDK'yi azaltabilir. Bu çalışmada LMK'de artmış viskozitenin BOS'ta düşük ADC değerlerine neden olup olmadığını araştırmak amaçlandı. Leptomeningeal metastazlı 31 olgu ve yaş ve cinsiyet uyumlu, beyin MRG'si normal 31 olgu çalışmaya dahil edildi. Her iki tarafta lateral ventrikül posteriorlarından ve lateral pterigoid kaslarından (LPK) GDK ölçümleri yapıldı. Bireysel ve cihaz-bağımlı farklılıkları engellemek için GDK oranı (=GDKBOS/GDKLPK) hesaplandı. Grupların GDKBOS ve GDK oranları karşılaştırıldı. LMK grubundaki GDKBOS ortalama değeri, kontrol grubundaki değerden, istatistiksel olarak düşük bulundu. LMK grubundaki ortalama GDKBOS/GDKLPK oranı da kontrol grubundaki değerden istatistiksel olarak daha düşüktü. ROC analizi, GDKBOS değeri için 2844 (sensitivite 51.61%, spesifite 96.77%, eğri altı alan 0.800) ve GDK oranı için 1.97 (sensitivite of 74.19%, spesifite 93.55, eğri altı alan 0.833) sınır değeri ortaya koydu. GDK değeri, LMK tanısı doğruluğunu artırmak için tamamlayıcı bir araç olarak kullanılabilir.

**Anahtar Kelimeler:** Leptomeningeal karsinomatozis, manyetik rezonans görüntüleme, difüzyon ağırlıklı görüntüleme, GDK değeri, beyin omurilik sıvısı, viskozite

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## 1. Introduction

Leptomeningeal carcinomatosis, (LMC) also known as carcinomatous meningitis, is caused by the spread of malignant cells to the leptomeninges and by their dissemination within cerebrospinal fluid (CSF) (1). LMC occurs in approximately 5% of patients with cancer (2). The cancers most commonly associated with LMC are leukemia, lymphoma, breast cancer, lung cancer, and malign melanoma (3). Early diagnosis of LMC could improve patient's quality of life (2,3). The diagnosis of LMC is made on the basis of one of the following three National Comprehensive Cancer Network criteria: 1-Cytologic findings demonstrating tumor cells in the CSF, 2-Radiological findings of LMC irrespective of clinical findings, 3-Clinical findings consistent with LMC and abnormal laboratory findings in the CSF (low glucose level and elevated white blood cell and protein levels) in a patient with a cancer (4).

CSF cytologic analysis is currently considered as the gold standard to confirm LMC (5). However, CSF cytology can be false negative despite multiple examinations. In addition, as an invasive examination, CSF cytology is not proposed as a common examination (3,5). When cytologic analysis does not reveal LMC, LMC can be diagnosed by contrast-enhanced (CE) magnetic resonance (MR) imaging alone (4,6). Leptomeningeal enhancement appears as a streakly pattern on MRI. Contrast enhanced T1 weighted image (WI) have long been the technique of choice for evaluating LMC (7). LMC can be easily visualized on CE FLAIR sequence allows for a clearer distinction between enhancing meninges and enhancing cortical veins becoming less clearly enhanced on FLAIR images (8). However, sensitivity is not as strong as it is expected.

Diffusion-weighted imaging (DWI) is an MR technique which allows the evaluation of water movement in tissues. This can be quantified by the apparent diffusion coefficient (ADC) value and low ADC values indicate restricted diffusion (9). Restricted diffusion could be related to an increased cell density and increased fluid viscosity (10).

Hong et al reported that a decreased ADC value of intraventricular fluid in pyogenic ventriculitis due to pleocytosis and the protein content of CSF. Therefore, they proposed that the ADC value might be a useful non-invasive method for the follow-up evaluation of ventriculitis as well as the diagnosis of it (11). With similar argument of their report, we hypothesized ADC ratios in LMC can be decreased due to increased fluid viscosity related to elevated factors such as cell count, total protein, lactate dehydrogenase, and several tumor-specific antigens.

This study aims to investigate whether increased CSF viscosity in LMC causes low ADC values in CSF and if so, low ADC values can be used as a non-invasive method for the diagnosis of LMC.

## 2. Materials and Methods

Ethics committee approval was received for this study from the ethics committee of Eskisehir Osmangazi University Non-Invasive Clinical Investigations Ethical Committee.

### Subjects

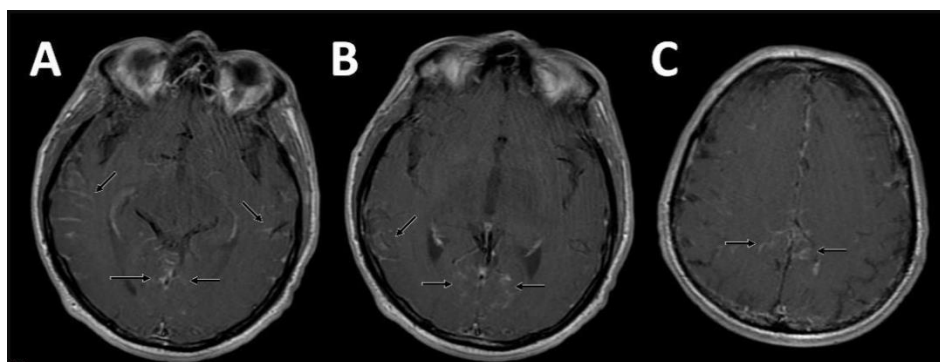
We retrospectively queried the radiology reports of brain MRI examinations performed between September 2010 and September 2019 using the keyword "leptomeningeal metastasis". Patients with both solid and hematological malignancies were included. Due to concomitant brain metastasis and previous radiation are significantly correlated with higher protein levels in the CSF, patients with brain metastasis and/or previous history of radiotherapy were excluded. LM enhancement is non-specific and can be observed in other condition including meningitis, subarachnoid hemorrhage, obstructive hydrocephalus, and in chances after surgery, radiation therapy, or intrathecal chemotherapy. Patients having at least one of these features were also not included.

For the controls, 31 subjects who were referred for headache and had had normal cranial MR images were randomly selected from a pool of patients.

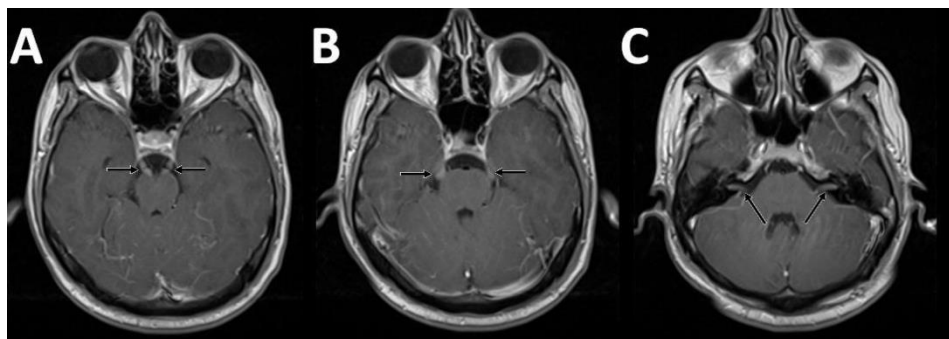
### MR Imaging and Analysis

MRI examinations were performed either on 1.5 Tesla MRI device (Magnetom vision plus, Siemens, Germany). on 3T MRI device (GE Healthcare, Waukesha, WI). The our conventional brain MRI protocol was as follows: T2-WI, fluid-attenuated inversion recovery imaging, non-enhanced T1-WI, Gd-DTPA contrast-enhanced T1-WI, DW. *Single-shot* echo-planar spin echo DW images was acquired with three *b* factors (0, 500 and 1000 s/mm<sup>2</sup>).

MRI images were transferred to the MR protocol workstation. From conventional MR images, a neuroradiologist with 12 years of experience, identified the LMC. A diagnosis of leptomenigeal carcinomatosis with diffuse leptomenigeal enhancement along the cerebral and cerebellar convexities and/or enhancement of the cranial nerves was made (Figure 1,2). DW images were separately analyzed by same neuroradiologists at different time.



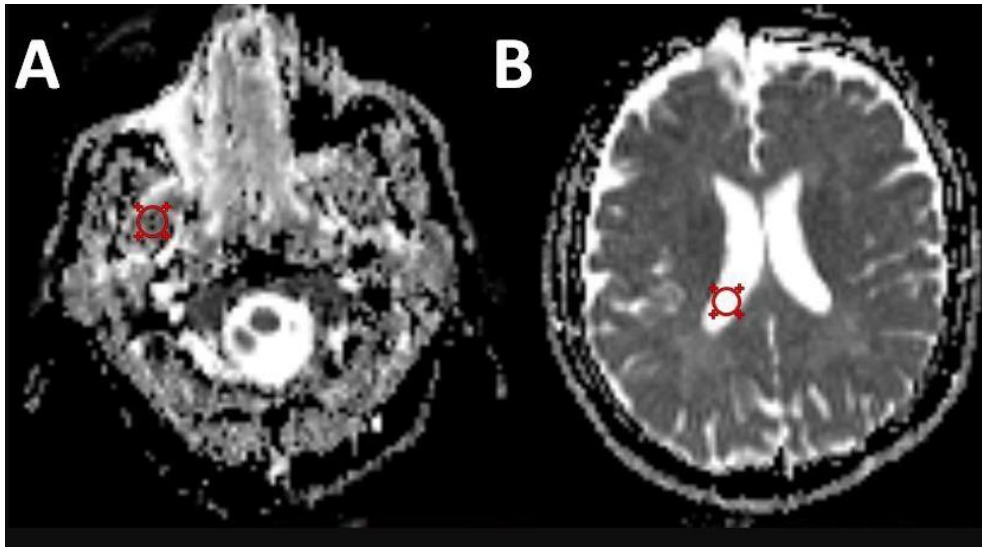
**Figure 1.** A-C. Postcontrast T1WI shows leptomenigeal enhancement representing LMC (arrows).



**Figure 2.** Postcontrast T1 WI demonstrates leptomenigeal enhancement of bilateral oculomotor nerve (A), trigeminal nerve (B), facial-vestibulocochlear nerve (arrows).

Measurements were made on both sides. We measured ADC values of CSF ( $ADC_{CSF}$ ) by manually placing regions of interest (ROIs) (at least 1cm in diameter) within posterior lateral ventricle body to avoid choroid plexus areas. Posterior lateral ventricle was preferred due to predominantly involvement of posterior areas in gravity-dependent regions according to Debnam study (7). ROIs were placed within lateral pterygoid muscle (LPM) to measure ADC value of LPM ( $ADC_{LPM}$ ) in

order to use it as a reference area outside of the brain (Figure 3). Mean ADCs were selected. The average ADC was calculated as the mean of the two ROIs obtained from right and left sides. The ADC ratio ( $=ADC_{CSF}/ADC_{LPM}$ ) was calculated by dividing the ADC values in the ROI by a reference ADC value which was obtained from IRC to prevent individual and device-dependent differences.



**Figure 3.** Round ROI is placed within the lateral pterigoid muscle in order to use it as a reference area outside of the brain (A) and within posterior lateral ventricle body to avoid choroid plexus areas (B).

### Statistical Analysis

ADCs and ADC ratios were compared between groups. All data analyses were conducted using the SPSS for Windows 22.0 (SPSS, Inc, an IBM Company, Chicago, IL) and Sigastat 3.5. Because the data were normally distributed, the Student t test was used to evaluate the differences between the groups in terms of ADCs and ADC ratios. All data were represented as the mean  $\pm$  SD. A values of  $P < 0.05$  were accepted as statistically significant. To evaluate the diagnostic performance of the ADCs for differentiating the LMC group and control group and to describe the sensitivity and specificity of the test, receiver operating characteristic (ROC) analysis was performed. The optimum cutoff point was determined as the value that best discriminates between the groups in terms of maximum sensitivity and minimum number of false-positive results.

### 3. Results

Thirty-one patients with LMC (21 men and 10 women; mean age 60.7 years; range 18–86

years) and 31 patients with normal brain MR imaging (21men, 10 women, mean age 57.8 years, range 18 to 73 years) were analyzed in the study. There were no age or gender differences between two groups. Underlying malignancies in the LMC group included acute myeloblastic leukemia (N 8), lung carcinoma (N 8), non-Hodgkin lymphoma (N 5), breast carcinoma (N 4), chronic myeloid leukemia (N 3), colon carcinoma (N 1), pancreatic carcinoma (N 1), and renal cell carcinoma (N 1).

The mean  $ADC_{CSF}$  ranged between 2238 and 3273 (mean,  $2835.58 \pm 240.52$ ) in the LMC group, between 2792 and 3807 (mean,  $3069.97 \pm 164.10$ ) in the control group. The mean  $ADC_{CSF}/ADC_{LPM}$  ratio ranged between 1.45 and 4.03 (mean,  $1.99 \pm 0.19$ ) in the LMC group, between 1.85 and 3.12 (mean,  $2.01 \pm 0.18$ ) in the control group. The mean  $ADC_{CSF}$  was lower in the LMC group than control group, with a statistically significant difference ( $P < 0.05$ ). The mean  $ADC_{CSF}/ADC_{LPM}$  ratio in the LMC group was lower than those in the control group with statistical significance ( $P < 0.05$ ).

Table shows a comparison of mean  $ADC_{CSF}$  and  $ADC_{CSF}/ADC_{LPM}$  ratios between two groups.

**Table.** Quantitative Analysis of Lateral Ventricle

	Leptomeningeal Carcinomatosis Group	Control Group	P
ADC <sub>CSF</sub>	2835.58 ± 240.52	1.91 ± 0.19	<b>0.028</b>
ADC <sub>CSF</sub> /ADC <sub>LPM</sub> ratio	3069.97 ± 164.10	2.01 ± 0.18	<b>0.020</b>

Data are mean ± SD

The area under the ROC curve was  $0.800 \pm 0.057$  ( $P < 0,0001$ ) for mean ADC<sub>CSF</sub> and  $0.833 \pm 0.057$  ( $P < 0,0001$ ) for mean ADC<sub>CSF</sub>/ADC<sub>LPM</sub> ratio, respectively. A cutoff value of 2844 for the mean ADC value generated the best combination of sensitivity (51.61%) and specificity (96.77%) for distinguishing between LMC and control groups. An optimal ADC ratio threshold of 1.97 for differentiating LMC from the control group. This cut-off showed a sensitivity of 74.19 % and specificity of 93.55 %.

#### 4. Discussion

LMC represents the spread of tumor cells through the CSF space (1). The incidence of LMC appears to be increasing due to advances imaging techniques. This is partially related to prolonged patient survival which increases the likelihood of developing metastases in unusual sites, but also due to the fact that water-soluble drugs that successfully treat systemic cancer cannot penetrate the brain-blood barrier (12). Early diagnosis of LMC is necessary to improve the quality of life patients (2,3). The examination of CSF has critical value for the diagnosis of LMC (12). When cytologic analysis does not reveal LMC, LMC can be noninvasively diagnosed by neuroimaging alone in the appropriate clinical setting (4,6). The MR abnormalities included pial-arachnoid metastatic disease, metastatic disease coating the nerves, hydrocephalus, subependymal metastasis. However, sensitivity is not as strong as expected. Singh et al showed that sensitivity and specificity of CE T1-weighted MRI for detection of LMC were 59% and 93% while the those of CE FLAIR were 41% and 88%, while respectively (6). For this reason, additional criterias required to increase diagnostic accuracy of LMC.

DWI is a functional MR technique based on measurement of the random Brownian motion within tissue voxel (13). The diffusion feature of a single voxel represents the combination of water diffusion in different compartments: diffusion within the intracellular space fluid (the cytoplasm and organelles); diffusion within extracellular space fluid (interstitial fluid, intravascular, lymphatic and various biological cavities) and diffusion between intra- and extra-cellular spaces. Increasing cellularity and viscosity inside those spaces result in the restriction of molecule-motion (14). DWI-derived ADC maps provide a quantitative measure of the degree of restricted diffusion. As a result of the disease, patients with LMC have CSF profiles with elevated factors such as cell count, total protein, lactate dehydrogenase, and several tumor-specific antigens. Since viscosity of CSF is higher in LMC, it is reasonable to expect that ADC value of CSF in LMC should be lower. In our study, when mean ADC<sub>CSF</sub> and ADC<sub>CSF</sub>/ADC<sub>LPM</sub> ratio were compared between the LMC group and the control group, we detected that both the mean ADC<sub>CSF</sub> and ADC<sub>CSF</sub>/ADC<sub>LPM</sub> ratio in the LMC group was lower than those in the control group with statistical significance. The decreased ADC values can be used as a non-invasive method for the diagnosis of LMC

This study has several limitations. First, the size of the sample was small. Secondly, we could not compared them with CSF cytological analysis because of the invasive nature of lumbar puncture. In addition, as all the quantitative measurements were taken by 1 radiologist, interobserver agreement of results could not be assessed.

In conclusion, we found that both the mean ADC<sub>CSF</sub> and ADC<sub>CSF</sub>/ADC<sub>LPM</sub> ratio in the

LMC group was lower than those in the control group with statistical significance. ADC value may be used as a complementary tool to increase diagnostic accuracy of LMC.

If further studies on larger series clarify the relationship between  $ADC_{CSF}/ADC_{LPM}$  ratio and LMC, ADC value should be used to increase diagnostic accuracy of LMC.

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