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Histogram Analysis Parameters Apparent Diffusion Coefficient for Distinguishing High and Low-Grade Meningiomas: A Multicenter Study

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Abstract

Low grade meningiomas have better prognosis than high grade meningiomas. The aim of this study was to measure apparent diffusion coefficient (ADC) histogram analysis parameters in different meningiomas in a large multicenter sample and to analyze the possibility of several parameters for predicting tumor grade and proliferation potential. Overall, 148 meningiomas from 7 institutions were evaluated in this retrospective study. Grade 1 lesions were diagnosed in 101 (68.2%) cases, grade 2 in 41 (27.7%) patients, and grade 3 in 6 (4.1%) patients. All tumors were investigated by MRI (1.5 T scanner) by using diffusion weighted imaging (b values of 0 and 1000 s/mm^2). For every lesion, the following parameters were calculated: mean ADC, maximum ADC, minimum ADC, median ADC, mode ADC, ADC percentiles P10, P25, P75, P90, kurtosis, skewness, and entropy. The comparison of ADC values was performed by Mann–Whitney-U test. Correlation between different ADC parameters and KI 67 was calculated by Spearman's rank correlation coefficient. Grade 2/3 meningiomas showed statistically significant lower ADC histogram analysis parameters in comparison to grade 1 tumors, especially ADC median. A threshold value of 0.82 for ADC median to predict tumor grade was estimated (sensitivity = 82.2%, specificity = 63.8%, accuracy = 76.4%, positive and negative predictive values were 83% and 62.5%, respectively). All ADC parameters except maximum ADC showed weak significant correlations with KI 67, especially ADC P25 ($P = -.340$, $P = .0001$).

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Introduction

Meningioma is the most frequent intracranial tumor in adults with a prevalence of 13–26% of all intracranial neoplasms and an annual incidence of 6 per 100 000 population [1]. According to the world health organization (WHO), there are three subgroups of meningiomas: low grade tumors (grade 1), moderately differentiated lesions (grade 2), and high grade or malignant tumors (grade 3) [1]. Most frequently (about 90%), WHO grade 1 tumors occur, whereas WHO

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grade 2 are in 5–7%, and anaplastic variants (WHO grade 3) represent 1–3% [1].

Magnetic resonance imaging (MRI) plays an important role in diagnosis of meningioma and in surgical planning and/or evaluation of postoperative status. Besides diagnostic role, MRI, especially diffusion weighted imaging (DWI) can also characterize meningiomas and predict their behavior. For example, some previous reports suggested that a quantified parameter of DWI, namely apparent diffusion coefficient (ADC) can differentiate low grade from high grade meningiomas [2–5]. It has been shown that grade 1 lesions had higher ADC values in comparison to grade 2 and/or 3 tumors [2–5]. Furthermore, also a threshold ADC value was proposed for distinguishing grade 1 and 2/3 tumors with a sensitivity of 72.9%, specificity of 73.1%, positive and negative predictive values of 54.1% and 86.1%, respectively [5].

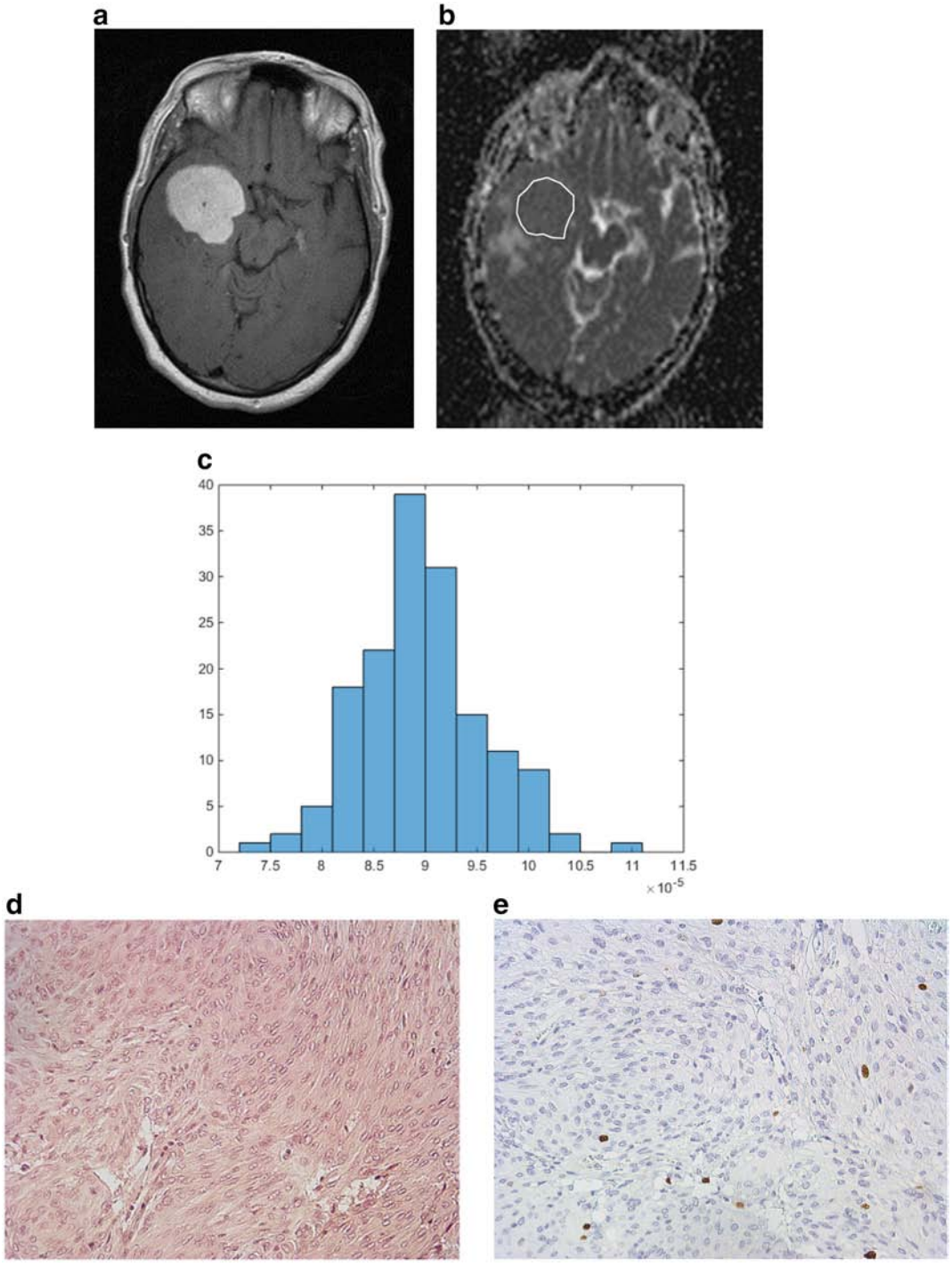

Figure 1. ADC histogram analysis parameters of a grade 1 meningioma. a. T1 weighted image after intravenous administration of contrast medium showing a right temporal meningioma. b. ADC map of the tumor with a ROI. c. ADC histogram. The histogram analysis parameters ($\times 10^{-3}$ mm^2 s^{-1}) are as follows: ADC_{min} = 0.74, ADC_{mean} = 0.89, ADC_{max} = 1.09, P10 = 0.83, P25 = 0.86, P75 = 0.93, P90 =0.98, median = 0.9, mode = 0.9, kurtosis = 3.25, skewness = 0.24, and entropy = 2.97. d. Histopathological investigation after tumor resection: meningothelial meningioma (hematoxilin&eosin staining). e. KI 67 index of the tumor is 5% (MIB staining).

In the previous studies, ADC was acquired by drawing of a region of interest (ROI) through the largest cross-section of the tumor and the mean ADC value within a ROI was estimated [2–5].

Nowadays, a novel approach of ADC measure, namely histogram analysis, is described in the literature [6]. Using this method, a broad spectrum of ADC values can be estimated: mean ADC, maximum ADC, minimum ADC, median ADC, mode ADC, and different ADC percentiles, as well and statistical parameters like kurtosis, skewness, and entropy [7]. Presumably, ADC histogram analysis parameters may be more sensitive than "conventional" ADC values in prediction of tumor grading and proliferation potential in meningiomas.

Therefore, the purpose of the present study was to measure of ADC histogram analysis parameters in different meningiomas in a large multicenter sample and to analyze the possibility of use of several parameters for predicting tumor grade and proliferation potential.

Material and Methods

Patients and Tumors

This retrospective study was initiated by the department of radiology of the Martin-Luther-university Halle-Wittenberg and has been approved by the Institutional (Ethic Committee of the Medical Faculty, Martin-Luther-university, study code: 2014–99). All methods were performed in accordance with the relevant guidelines and regulations. Because of the retrospective nature of this study, informed consent was waived.

For this study, data from 7 radiology departments were acquired retrospectively, including the following centers:

- Department of Radiology, Martin-Luther-University Halle-Wittenberg, Germany;
- Department of Radiology, University of Chicago, Pritzker School of Medicine, Chicago, IL, USA;
- Department of Neuroradiology, National Neuroscience Institute, Singapore;
- Clinic for Neuroradiology, Katharinen Hospital Stuttgart, Stuttgart, Germany;
- Servicio de Radiologia, Hospital de Navarra, Pamplona, Spain;
- Department of Radiology, School of Medicine, Istanbul Medipol University, Istanbul, Turkey;
- Department for Neuroradiology, University Hospital Leipzig, Leipzig, Germany;

The primary sample consisted of 219 tumors. Inclusion criteria were as follows:

- primary tumors,
- tumor size >10 mm,
- available ADC maps,
- available data about tumor grade,
- available data about expression of KI 67.

Overall, 71 tumors were excluded because the following reasons: 11 lesions were recurrent tumors, for 19 meningiomas no ADC maps were available, no tumor grading was given for 7 tumors, 9 meningiomas were smaller than 10 mm in diameter and could not be identified on ADC maps, finally, ADC maps showed significant artifacts in 25 tumors.

Therefore, our study comprised 148 meningiomas in 148 patients (94 women, 54 men; mean age 52.2 ± 14.0 years, range, 5–91 years). All 148 meningiomas were surgically resected and analyzed histopathologically. Tumor grading was classified according to the World Health Organization [1]. Grade 1 lesions were diagnosed in 101 (68.2%) cases, grade 2 in 41 (27.7%) patients, and grade 3 in 6 (4.1%) patients.

ADC Histogram Measurement

In each case the identified meningioma was investigated by MRI (1.5 T scanner) by using DWI (multi-shot echo-planar-imaging sequence with b values of 0 and 1000 s/mm^2).

ADC images of the included tumors were saved in DICOM format and processed offline with custom-made Matlab-based application (The Mathworks, Natick, MA) on a standard windows system according to our previous description [7]. In every case, polygonal regions of interest (ROI) were manually drawn on the transferred ADC maps along the contours of the primary tumor on each slice (whole lesion measure). ROIs were placed to avoid cystic and necrotic areas as well as large vessels of the tumors. All measurements were performed by one radiologist (A.S., 15 years radiological experience). The position of the ROIs was verified using postcontrast T1 weighted images (Figure 1, *A* and *B*). The following parameters were calculated: mean ADC (ADC_{mean}), maximum ADC (ADC_{max}), minimum ADC (ADC_{min}), median ADC (ADC_{median}), mode ADC (ADC_{mode}). Furthermore, ADC percentiles: 10th (P10 ADC), 25th (P25 ADC), 75th (P75 ADC), and 90th (P90 ADC), as well histogram-based characteristics of the ROIs - kurtosis, skewness, and entropy – were also estimated (Figure 1*C*) [7].

Statistical Analysis

For statistical analysis the SPSS statistical software package was used (SPSS 17.0, SPSS Inc., Chicago IL, USA). All measurement were non-normally distributed according to Kolmogorov–Smirnov-test. Continuous variables were described by mean value, median and standard deviation. Categorical variables were given as relative frequencies. The comparison of ADC values between high and low grade tumors was performed by Mann–Whitney -U tests where the p-values are adjusted for multiple testing (Bonferroni correction). The correlation between different ADC parameters and KI 67 values was calculated by Spearman's rank correlation coefficient (p). Sensitivity, specificity, negative and positive predictive values, accuracy, and area under the curve were calculated for the diagnostic procedures. Thresholds were chosen to maximize the Youden index. A P-value of less than 0.05 was considered to be statistically significant.

Results

ADC Values and Tumor Grading

Grade 2/3 meningiomas showed statistically significant lower ADC histogram analysis parameters in comparison to grade 1 tumors (Table 1).

On the next step, different ADC values were checked for possibility to distinguish grade 1 from grade 2/3 lesions. Receiver operating characteristic (ROC) analysis (Figure 2 and Table 2) showed that ADC median was more sensitive in comparison to other parameters.

Table 1. Comparison of ADC Histogram Analysis Parameters Between Grade 1 and Grade 2/3 Tumors

Parameters	Grade 1	Grade 2/3	*P* values
ADC_{mean}	0.99 ± 0.74	0.86 ± 0.23	0.004
ADC_{min}	0.75 ± 0.89	0.59 ± 0.22	0.008
ADC_{max}	2.17 ± 3.00	1.51 ± 0.62	0.009
ADC P10	0.94 ± 1.00	0.76 ± 0.21	0.001
ADC P25	1.06 ± 1.26	0.81 ± 0.21	0.004
ADC P75	1.21 ± 1.45	0.95 ± 0.26	0.005
ADC P90	1.40 ± 1.80	1.25 ± 1.00	0.07
ADC_{median}	1.00 ± 1.59	0.81 ± 0.22	0.001
ADC_{mode}	1.19 ± 1.55	0.85 ± 0.22	0.003
Kurtosis	8.11 ± 8.92	7.96 ± 9.51	0.52
Skewness	1.05 ± 1.27	1.08 ± 1.17	0.74
Entropy	3.57 ± 1.26	3.65 ± 0.89	0.77

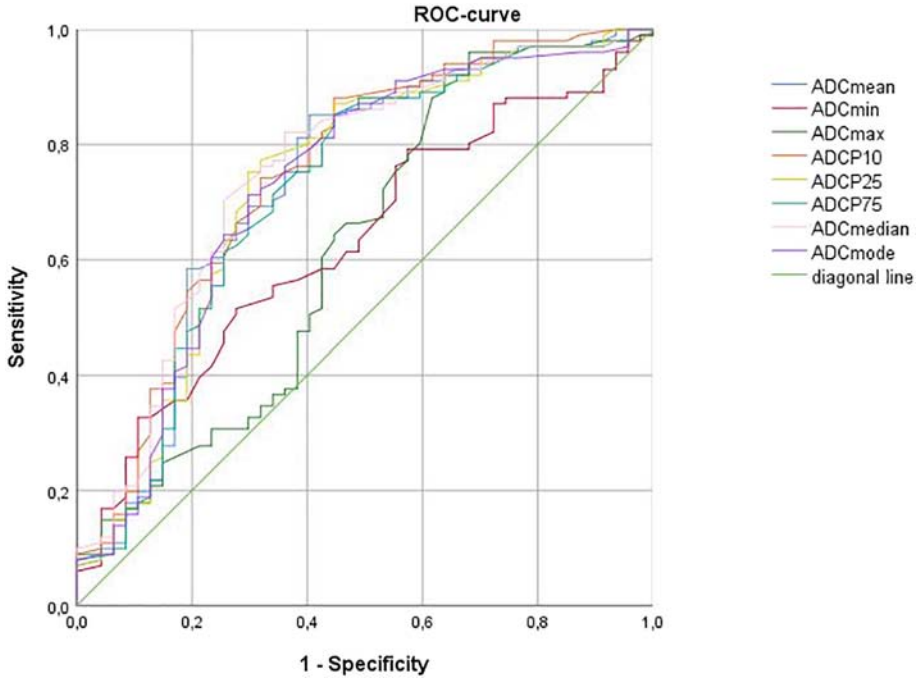

Figure 2. Receiver operating characteristic (ROC) curves for ADC histogram analysis parameters in distinguishing grade 1 meningiomas from grade 2/3 tumors.

Using Youden index a threshold value of 0.82 for ADC_{median} was identified. This threshold yielded a sensitivity of 82.2%, a specificity of 63.8%, and an accuracy of 76.4%. The positive and negative predictive values were 83% and 62.5%, respectively.

Table 2. Area Under the Curve for Different ADC Histogram Analysis Parameters as Predictor of Tumor Grade

Parameters	Area Under the Curve
ADC_{mean}	0.733
ADC_{min}	0.63
ADC_{max}	0.62
ADC P10	0.749
ADC P25	0.73
ADC P75	0.72
ADC P90	0.72
ADC_{median}	0.751
ADC_{mode}	0.73

Table 3. Correlation Coefficients Between ADC Histogram Analysis Parameters and Expression of KI 67 in Meningioma

Parameters	Correlation coefficients
ADC_{mean}	***P* = –.322 (*P* = .0001)**
ADC_{min}	***P* = –.209 (*P* = .011)**
ADC_{max}	*P* = –.054 (*P* = .513)
ADC P10	***p* = –.322 (*P* = .0001)**
ADC P25	***p* = –.340 (P = .0001)**
ADC P75	***P* = –.314 (P = .0001)**
ADC P90	***p* = –.263 (*P* = .001)**
ADC_{median}	***P* = –.329 (P = .0001)**
ADC_{mode}	***P* = –.333 (P = .0001)**
Kurtosis	*P* = .072 (*P* = .384)
Skewness	*P* = .115 (*P* = .165)
Entropy	*P* = .083 (*P* = .315)

Significant correlations are highlighted in bold.

KI 67 Status

The level of the proliferation index Ki 67 was available for all 148 patients. The mean value of KI 67 expression was 6.84 ± 6.67%, range 1–38%, and median value of 5%. Most of histogram analysis parameters showed significant correlations with KI 67 expression ranging from *P* = –.34 (*P* = .0001) for ADC p25 to *P* = –.263 (*P* = .001) for ADC P90 (Table 3).

Next, ROC analysis was performed for differentiating tumors with high proliferative potential from tumors with low expression of KI 67 using ADC values (Table 4). Based on the results, ADC P25 was selected for further analysis. Table 5 shows ROC analysis parameters for ADC P25 using different threshold values of KI 67 expression.

Discussion

This is the first multicenter study that evaluates relationships between ADC histogram analysis parameters and tumor grade/proliferation activity in meningioma.

According to the literature, ADC histogram analysis parameters can reflect different histopathological features in several tumors [8–11]. It has also been shown that ADC histogram analysis parameters were more sensitive in comparison to widely used mean and/or minimal ADC

Table 4. Area Under the Curve for Different ADC Histogram Analysis Parameters as Predictor of KI 67 Expression

Parameters	Area Under the Curve
ADC_{mean}	0.635
ADC_{min}	0.588
ADC_{max}	0.496
ADC P10	0.628
ADC P25	0.647
ADC P75	0.635
ADC P90	0.607
ADC_{median}	0.638
ADC_{mode}	0.646

Table 5. Receiver Operating Characteristic (ROC) Analysis for ADC P25 as Predictor of KI 67 Expression

KI 67, %	Threshold Values	Sensitivity	Specificity	Area Under the Curve	Positive Predictive Value	Negative Predictive Value	Accuracy
Ki67< 5%	0.78	0.806	0.519	0.647	0.581	0.764	0.649
Ki67< 10%	0.78	0.752	0.674	0.701	0.849	0.527	0.730
Ki67< 15%	0. 78	0.688	0.750	0.761	0.946	0.273	0.696
Ki67< 20%	0.73	0.826	0.600	0.714	0.966	0.200	0.811

values [9–11]. For instance, in thyroid cancer, several parameters correlated statistically significant with expression of tumor suppressor protein p53 [9]. Furthermore, in cervical cancer, ADC histogram analysis parameters can predict lymph node metastases: nodal-positive tumors showed statistically significant lower ADC percentiles (10th, 25th, 50th, 75th, 90th), as well ADC_{min}, ADC_{mean}, ADC_{median} and ADC_{mode} values in comparison to nodal-negative carcinomas [10]. Finally, ADC histogram analysis parameters were associated with expression of p53, proliferation index KI 67, epidermal growth factor receptor and with programmed cell death protein PD1 [11]. Overall, the reported data suggest that ADC histogram analysis is a sensitive instrument to predict tumor behavior in several malignancies.

The present study showed that also in meningioma parameters of ADC histogram analysis can reflect relevant histopathological features. As shown, grade 2/3 meningiomas had statistically significant lower several ADC values in comparison to grade 1 tumors. These results confirmed our previous investigations [5]. Moreover, two parameters, namely ADC_{median} and ADC P10 were more sensitive in comparison to other ADC values and can distinguish grade 1 meningiomas from grade 2/3 tumors with higher sensitivity than those previously reported for ADC mean [5]. Recently, it has been shown that entropy of ADC values may be used for prediction of tumor grade in meningioma [12]. Our results did not confirm these data.

Furthermore, our study identified that several ADC histogram analysis parameters correlated weakly with KI 67 expression. KI 67 is a non-histone, nuclear protein synthesized throughout the whole cell cycle except the G0 phase and it is one of numerous proliferation markers that play a significant role in meningiomas [1]. For example, meningiomas that recur tend to have higher KI 67 expression than those that do not [1]. Our finding is in agreement with previous reports, which also observed weak-to-moderate correlations between ADC, namely ADC_{mean}, and KI 67 [2,13]. However, the present study showed that ADC P25 may better predict tumors with high proliferation activity than other parameters.

As reported previously, prediction of tumor grade of meningiomas based on imaging findings is very important [5,14,15]. Meningioma is the most frequent intracranial tumor and is often an incidental finding on imaging. Therefore, it is relevant to know what tumor grade is present [5,14]. Furthermore, it is also crucial for surgical planning [14]. Similarly, it is of importance to differentiate tumors with high and low proliferation activity. Previously, numerous studies attempted to build scores to predict tumor grade in meningioma based on different imaging modalities [15–18]. Especially MRI findings were in focus of the investigations. The analyses included MRI characteristic like enhancement intensity, tumor associated brain edema, and tumor shape [15]. For example, in the study of Lin et al. a score, which included patient's age, tumor-brain interface, tumor enhancement, and capsular enhancement, was proposed [15]. However, these analyses are investigator-dependent. Furthermore, the reported scores had low sensitivity and/or specificity.

Ultimately, ADC histogram analysis can serve as a quantitative imaging biomarker that can be implemented in routine clinical practice.

In conclusion, ADC histogram analysis can be used for prediction of tumor grade and proliferation potential of meningioma. In particular, ADC_{median} can differentiate grade 1 meningioma from grade 2/3 tumors and ADC P25 may help to identify tumors with high proliferation activity.

Conflict of Interest

There are no conflicts of interest.

Additional Information

Competing Interests statement.

The authors declare no competing interests.

Author Contributions

1. **Conceptualization:** AS
2. **Data curation:** AS, DTG, TL, TC, OB, GAG, DHR, GH
3. **Formal analysis:** AS, AW, KTH
4. **Investigation:** AS, SS, HJM.
5. **Methodology:** AS, HJM, AW.
6. **Project administration:** AS.
7. **Resources:** AS, HJM, SS.
8. **Software:** HJM, AS, SS.
9. **Supervision:** KTH, AS.
10. **Validation:** AS, HJM, SS.
11. **Visualization:** SS, AS, HJM.
12. **Writing – original draft:** AS.
13. **Writing – review & editing:** KTH, SS, AS, TL, TC, OB, GAG, DHR, GH.

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