European Review for Medical and Pharmacological Sciences 2022; 26: 846-852

Use of multiparametric magnetic resonance imaging as a screening tool for the determination of acute ischemic stroke duration

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Abstract. – OBJECTIVE: This study aimed to assess the usability of magnetic resonance imaging (MRI) parameters in the treatment of stroke patients whose symptom onset time is unknown.

PATIENTS AND METHODS: We evaluated MRI of the patients whose stroke symptoms began within 12-hours. For quantitative analysis, fluid-attenuated-inversion-recovery (FLAIR) and diffusion-weighted-imaging (DWI) signal-intensity-ratios (SIR) of the lesions were computed. For qualitative analysis, 'mismatch' between visibility of lesion on DWI-FLAIR was evaluated. Patients were analyzed according to the first 4.5/6 hours of stroke onset time.

RESULTS: There was a moderate (r=0.569, *p*<0.001) correlation between symptom MRI time and FLAIR SIR and a weak correlation with DWI SIR (r=0.355, *p*=0.001). A FLAIR SIR threshold of ≤1.18 for predicted symptom onset 4.5 hours increased specificity (0.77 *vs.* 0.74) and sensitivity (0.77 *vs.* 0.69) as compared with visual analysis. A FLAIR SIR threshold of ≤1.19 for predicted symptom onset 6 hours increased sensitivity (0.76 *vs.* 0.67) and equal specificity (0.75 *vs.* 0.75) as compared with visual analysis.

CONCLUSIONS: In hyperacute ischemic stroke, lesion age can be determined more accurately by the FLAIR SIR analysis than visual analysis. In patients whose stroke onset time is unknown, the FLAIR SIR can be used as a biomarker in the management of stroke patients.

Key Words:
Ischemic stroke, FLAIR, DWI, Signal-intensity-ratio.

Introduction

Studies[1,2] have revealed that for approximately one-fourth of patients presenting with acute stroke, the time of onset was not able to be determined. The unknown time of symptom onset causes many patients presenting with acute stroke to miss the opportunity to be treated with intravenous (IV) recombinant tissue plasminogen activator (tPA). Therefore, a method that allows the determination of the symptom onset period is needed so that patients with unknown symptom onset time can be treated.

The mismatch between diffusion weighted imaging (DWI) and fluid-attenuated inversion recovery (FLAIR) sequences from magnetic resonance imaging (MRI) has been used in several studies for the estimation age of acute ischemic cerebral lesions[3-6]. In DWI, the ischemic lesion becomes hyperintense in minutes, whereas in FLAIR imaging, the signal intensity does not get hyperintense up to hours after the onset of ischemia[4,6]. The reason for the signal intensity to increase hours later in the FLAIR sequence has been shown as vasogenic edema due to disruption of the blood-brain barrier by ischemia[3-6]. FLAIR intensities can be determined as negative, slight, or bright based on a qualitative evaluation. However, studies[3-6] have shown that the evaluation made with the visual technique has low positive/negative predictive value and sensitivity. There are studies showing that the calculation of the FLAIR signal intensity ratio (SIR) of the ischemic lesion with the quantitative analysis method has higher negative/positive predictive value and sensitivity in determining the age of the lesion[7,8]. However, as far as we know, there are few studies in the literature to determine the age of the infarct lesion based on quantitative analysis with FLAIR and DWI signal intensity ratio[7-9]. Therefore, there is a need for new studies that reveal the age of the ischemic lesion more accurately than visual analysis.

The aim of this study is to characterize the signal intensity in FLAIR and DWI images with

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both qualitative and quantitative methods, to determine the age of stroke lesion, and to demonstrate its usability for the treatment of patients whose symptom onset time is unknown.

Patients and Methods

Patient Selection

We retospectively evaluated the patients who applied to Adıyaman University training and research hospital with ischemic stroke symptoms between January 2017 and March 2020 and met the inclusion criteria.

Inclusion criteria for the study were known onset acute stroke symptoms and DWI with FLAIR MR images within 12 hours. Exclusion criteria from the study were unknown or uncertain acute stroke symptom onset time, patients with hemorrhage on CT, patients with additional pathology on MRI (large encephalomalacia sequelae, history of operation, extensive chronic ischemic white matter changes, etc.), and those with artifacts on MRI. After the exclusion criteria, 82 patients who met the inclusion criteria were evaluated. The study was approved by the Adıyaman University Ethical Commitee.

Demographic characteristics such as gender, age, risk factors and stroke age, time from the beginning of stroke symptoms till MRI, modified Ranking score (mRS) and National Institutes of Health Stroke Scale (NIHSS) at admission of the patients who were included in the study, were recorded. The patients who came in the first 4.5 hours were given IV tPA treatment. However, since there are studies applying this treatment in patients who come in the first 6 hours, the patients were analyzed by grouping them according to two different values, the first 4.5 hours and the first 6 hours, according to the time elapsed between stroke onset time and imaging[10,11].

Image Analysis of MRI

Quantitative Analysis of MRI

The location of the acute ischemic lesion was determined by evaluation with DWI sequences. The lesion location and intensity detected by DWI were evaluated by examining FLAIR sequence images. A section of the FLAIR sequence was selected to represent the areas where signal intensity was most visible in the lesion location. If the acute ischemic lesion was invisible on the FLAIR sequence images, on the FLAIR sequence images we selected the regions and sections that best corresponded to the ischemic lesion region in the DWI sequence. We calculated the FLAIR SIR value by dividing the signal value in the corresponding region in the FLAIR sequence of the ischemic lesion in the DWI slice by the FLAIR signal value in the normal opposite side of the cerebrum at the same level. The DWI SIR value was calculated by dividing the DWI signal intensity in the normal opposite side of the cerebrum at the same level of the ischemic lesion in the DWI slice. The ADC value was calculated on the console from the ADC map image of the ischemic lesion.

Qualitative Analysis of MRI

For qualitative analysis, the equivalent of the lesion observed in the DWI sequence was evaluated visually in the FLAIR sequence. The ischemic lesion detected in the DWI sequence was examined according to the intensity of the FLAIR sequence as bright, slight, and no hyperintensity, and in statistical analysis, it was evaluated in two groups as positive (bright and slight) and negative according to FLAIR intensity (Figure 1). Images were evaluated by two readers with 6 and 8 years of MRI reading experience. This assessment was used for interobserver analysis. Images with discordance between these two observers were analyzed by a third reader with over 20 years of MRI reading experience, and this final evaluation was used to evaluate the visual analysis results.

MRI Protocol

A 1.5-T whole-body MRI system (Achieva; Philips Medical Systems, Best, The Netherlands) was used for all MRI examinations. DWI images were acquired with a single-shot echoplanar sequence (imaging parameters: repetition time, 3056 ms; echo time, 73 ms; matrix, 152×106; viewing field, 23 cm; gap, 1 mm; slice thickness, 5 mm; EPI factor 53; and acquisition time, 1.04 min. FLAIR images were performed with a 23-cm viewing field and 5-mm thick sections with a 1-mm gap, matrix of 216×130, and repetition time/echo time/ inversion time 6000/100/2000 ms, and acquisition time, 1.30 min.

Statistical Analysis

Statistical analysis was performed to evaluate the predictive power of the data obtained after the quantitative and qualitative evaluation of the

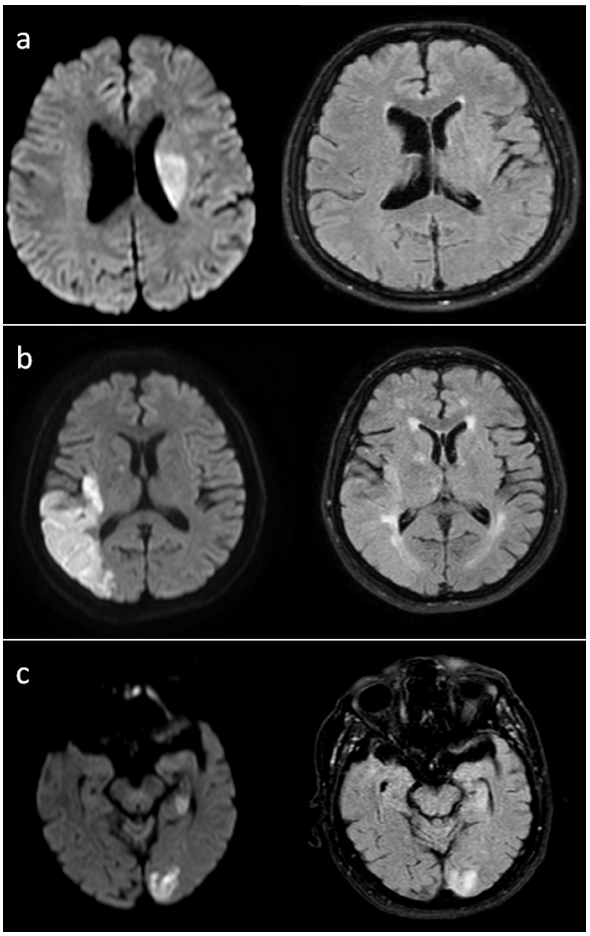

Figure 1. Examples of ischemic lesions; Diffusion-weighted imaging (DWI) images show acute ischemic lesions (left column). Corresponding intensity patterns appear in the Fluid-attenuated inversion recovery images (FLAIR) images (right column); no hyperintensity **(a)**, slight hyperintensity **(b)**, bright hyperintensity **(c)**.

patients' symptom onset times to MRI in 4.5 and 6 hour time windows. The relationship between the time from symptom onset to MRI and quantitative data (FLAIR SIR and DWI SIR) was evaluated with the Spearman correlation test. Quantitative data analyses were made with the normality distribution Kolmogorov-Smirnov test. Independent samples *t*-test or Mann-Whitney U test was used to compare two groups according to normality distribution. ROC analysis was performed for parameters that differed significantly between the groups, and sensitivity, specificity, NPV, and PPV were calculated according to the optimal cutoff value. The chi-square test was used to evaluate the qualitative analysis results. In addition, the kappa value was used to evaluate the interrater agreement in the qualitative analysis results. A *p*-value of <0.05 was accepted as statistically significant. All statistical analyses were carried out using the Statistical Package for Social Sciences program, version 23.0 (IBM, Armonk, NY, USA).

Results

Patient Characteristics

The mean age of the patients was 67.54 ± 13.54 years, the median NIHSS score at admission was 7 (interquartile range, 4-12), and 52.4% (n=43) were male. While the median time from stroke onset to MRI was 130 minutes (min-max, 30-210) in patients admitted in the first 4.5 hours, it was 600 minutes (min-max, 300-720) in patients admitted after 4.5 hours. Stroke was caused by anterior circulation in 78% (n=64) of the patients. According to the time from the onset of stroke to MRI, the data of the patients categorized as less than 4.5 hours and above are as seen in Table I.

Qualitative Analysis

In the FLAIR sequence imaging of the patients, in the first 4.5-hour group, 69.8% (n=30) had no hyperintensity, 20.9% (n=9) had slight hyperintensity and 9.3% (n=4) had bright hyperintensity. In patients over 4.5 hours, 25.6% (n=10) had no hyperintensity, 35.9% (n=14) had slight hyperintensity and 38.5% (n=15) had bright hyperintensity. In FLAIR intensity evaluation, the interrater fit was moderate to good (κ = 0.627; 95% CI: 0.481-0.772).

A significant difference was found between the groups in the chi-square analysis performed to evaluate the effectiveness of visually assessed negative FLAIR hyperintensity in differentiating 4.5 and 6 hours of time to MRI (p <0.001 (χ^2= 15.938), p <0.001 (χ^2= 14.525, respectively). The sensitivity, specificity, NPV, and PPV of the qualitative analysis for both time windows are given in Table II.

Quantitative Analysis

For the 82 patients included in the study, there was a moderate (r = 0.569, p < 0.001) correlation between symptom MRI time and FLAIR SIR and a weak correlation with DWI SIR (r = 0.355, p = 0.001), while no significant correlation was found with ADC value (r = -0.146, p = 0.192).

In the evaluation of the symptom MRI time grouped according to the first 4.5-hour time zone, a significant difference was found between the groups in the FLAIR SIR (z =-5.725, p < 0.001)

Table I. Demographic data of patients according to 4.5 hours, qualitative and quantitative analysis results.

	Under 4.5 hours	Over 4.5 hours	*p*-value (test statistic result)
Age (years)*			0.131 (z = -1.510)
Mean ± SD	70 ± 12.48	64.82 ± 14.29	
Median (min-max)	72 (38-96)	67 (29-91)	
Female#	22/43 (51.2%)	17/39 (43.6%)	0.493 (X^2 = 0.470)
NIHSS score on admision*			0.001 (z = -3.242)
Mean ± SD	10 ± 5.31	6.44 ± 3.78	
Median (min-max)	8 (2-20)	6(2-16)	
mRS*			0.003 (z = -2.952)
Mean ± SD	3.19 ± 1.24	2.31 ± 1.26	
Median (min-max)	3 (1-5)	2 (1–5)	
Time to MRI*			< 0.001 (z = -7.795)
Mean ± SD	127.91 ± 55.13	575.38 ± 116.76	
Median (min-max)	130 (30–210)	600 (300-720)	
FLAIR visual qualitative analysis#			< 0.001 (X^2 = 15.938)
• Negative	30 (69.8%)	10 (25.6%)	
• Positive	13 (30.2%)	29 (74.4%)	
Slight hyperintensity	9 (20.9%)	14 (35.9%)	
Bright hyperintensity	4 (9.3%)	15 (38.5%)	
FLAIR-SIR*			< 0.001 (z =-5.725)
Mean ± SD	1.11 ± 0.76	1.28 ± 0.13	
Median (min-max)	1.08 (1-1.28)	1.26 (1.06-1.54)	
DWI-SIR£			0.002 (*t* = -3.203)
Mean ± SD	0.53 ± 0.14	0.49 ± 0.13	
Median (min-max)	0.55 (0.22-0.92)	0.50 (0.27-0.84)	
ADC-value£			0.538 (*t* = 1.461)
Mean ± SD	364.05 ± 93.74	332.69 ± 100.59	
Median (min-max)	363 (221-662)	331 (172-62)	

mRS: Modified Rankin scale, SIR: Signal intensity ratio, SI: Signal intensity, *Mann-Whitney U test, #Pearson Chi-Square test, £Student's *t*-test.

and DWI SIR (t = -3.203, $p = 0.002$) values, while there was no significant difference between the groups in the ADC values (t = 1.461, $p = 0.538$) (Table I). In the evaluation of the symptom MRI time grouped according to the first 6-hour time zone, a significant difference was found between the groups between the FLAIR SIR (z =-5.635, $p < 0.001$) and DWI SIR (t = -3.577, $p = 0.001$)

Table II. Sensitivity, specificity, negative and positive predictive values of quantitative and qualitative analysis for 4.5 and 6 hours.

	Cutoff level	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)	*p*-value
Up to 4.5 hours						
• FLAIR-SIR	≤ 1.18	77% (61-87)	77% (60-88)	79% (62-89)	75% (58-87)	< 0.001 (X^2 = 23.575)
• DWI-SIR	≤ 1.55	60% (44-74)	71% (54-84)	70% (52-83)	62% (46-75)	0.003 (X^2 = 8.595)
• Qualitative analysis	+/-	69% (53-82)	74% (57-86)	75% (58-86)	69% (52-81)	< 0.001 (X^2 = 15.938)
Up to 6 hours						
• FLAIR-SIR	≤ 1.19	76% (61-87)	75% (57-87)	80% (64-90)	71% (53-84)	< 0.001 (X^2 = 21.196)
• DWI-SIR	≤ 1.56	63% (47-76)	69% (51-83)	72% (55-84)	59% (43-73)	0.004 (X^2 = 8.531)
• Qualitative analysis	+/-	67% (51-80)	75% (57-87)	77% (61-88)	64% (47-78)	< 0.001 (X^2 = 14.525)

SIR: Signal intensity ratio, +/-: positive/negative hyperintensity on FLAIR image.

values, while no significant difference was found between the groups in the ADC values (t = 1.165, $p = 0.102$).

ROC analysis graphs for FLAIR SIR and DWI SIR for both time windows are shown in Figure 2. In the 4.5-hour window, AUC for FLAIR SIR was 0.868 (95% CI, 0.792-0.943; $p < 0.001$) and AUC for DWI SIR was 0.683 (95% CI, 0.565-0.801; $p = 0.004$), while in the 6-hour window, the AUC for FLAIR SIR was 0.864 (95% CI, 0.784-0.944; $p < 0.001$), and the AUC for DWI SIR was 0.706 (95% CI, 0.589-0.822; $p = 0.001$). By ROC analysis, the optimum FLAIR SIR and DWI SIR thresholds for patients below 4.5 hours from stroke onset were ≤1.18 and ≤1.55, respectively while for patients less than 6 hours after stroke onset the optimum FLAIR SIR and DWI SIR thresholds were determined as ≤1.19 and ≤1.56, respectively, and the sensitivity, specificity, NPV, and PPV values for these values are given in Table II.

Discussion

IV tPA is used as an effective treatment method in the first 4.5 hours in patients with acute ischemic stroke[12]. Some scholars[10] have shown that this treatment can be performed for up to 6 hours. However, in order to carry out this treatment, it is necessary to know the exact onset time of the stroke symptom[11]. In approximately one quarter of stroke patients, it is not possible to determine this period[3-7]. For this reason, there are studies that try to determine the age of the ischemic lesion using multiparametric MR imaging and methods such as DWI-FLAIR mismatch[3-7]. However, it has been shown that among these studies, those performed with the qualitative method have lower sensitivity and specificity and PPV values compared to the quantitative ones[3,4,6]. Low agreement between observers and cases showing slight signal characteristics in the FLAIR sequence has been shown as a reason for this situation[3,4,6,7,9,13].

The findings obtained in our study show that there is a significant positive correlation between the SIR values measured from the FLAIR sequence and the time elapsed from symptom onset. This positive correlation supports the view that there is a linear increase in T2-FLAIR signal intensity with time of stroke onset[7]. In our study, we found that SIR ≤ 1.18 on the FLAIR sequence could indicate that stroke occurred within the 4.5-hour treatment window with a sensitivity of 77% (95% CI, 78%-90%) and specificity of 77% (95% CI, 65%-73%). In the studies conducted by Legge et al[7] and Song et al[8], these values were found to be FLAIR SIR ≤ 1.15 and were consistent with our study. These results show that it may be possible to use hyperintensity in the FLAIR sequence as a biological marker in cases where the onset of stroke symptom is unclear.

During acute stroke, the absence of intensity in the FLAIR sequence can be easily evaluated as a qualitative method. Previous studies have reported that while the stroke lesion is visible in the DWI sequence but not in the FLAIR sequence (DWI-FLAIR mismatch), it is a successful way

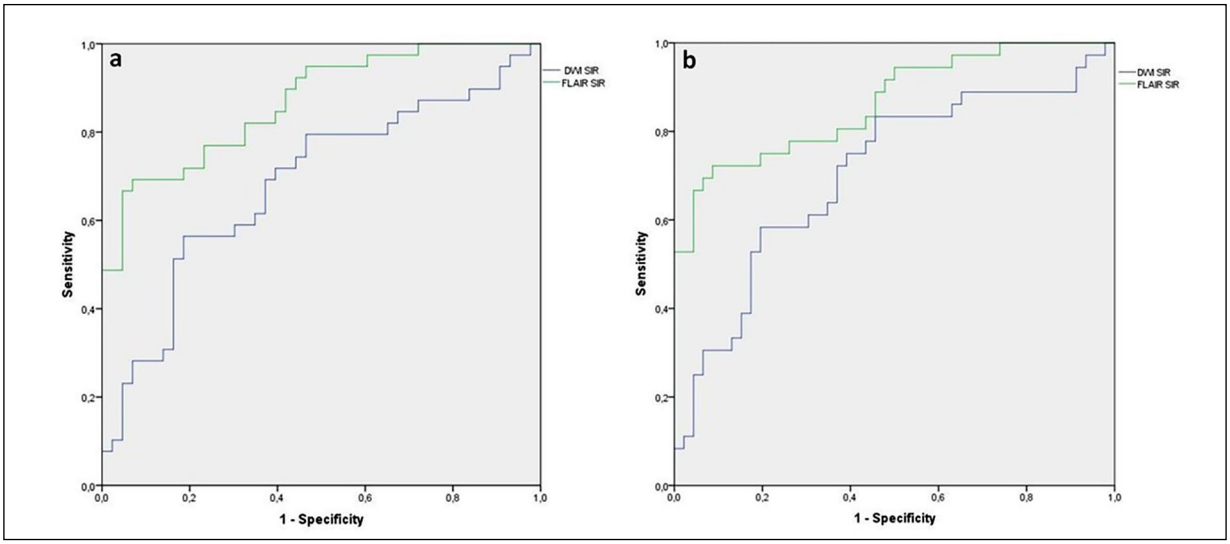

Figure 2. Receiver operating characteristic curve analysis for the first 4.5 **(a)** and 6 **(b)** hours from symptom onset till MRI.

of showing the safe time interval in which IV tPA treatment can be given[3-8,13]. The findings in our study show that, similar to those in other studies, the absence of any hyperintensity in the FLAIR sequence can accurately predict the lesion age in the 4.5-hour treatment window with 0.69 sensitivity and 0.74 specificity, 0.79 PPV, and 0.75 NPV. However, the sensitivity and specificity and PPV rates in the qualitative method are lower than the quantitative method and are consistent with the findings of other studies[3,4,6,12].

In our study, in the FLAIR sequence, 30% of patients had slight or bright positive signal intensity within the first 4.5 hours after symptom. In the study by Legge et al[7], this rate was found to be 38%. In the study by Petkova et al[4], patients with slight FLAIR hyperintensity were included in the same group as hyperacute patients who had no hyperintensity in FLAIR. Therefore, the sensitivity and specificity in the qualitative visual evaluation were found to be low. Similarly, in our study and that by Legge et al[7], if the cases with slight hyperintensity increase are included in the hyperacute stroke group, the sensitivity and specificity in the qualitative visual evaluation is found to be low. In this case, if the cases showing this positive signal increase are not included in the hyperacute ischemia group based only on the findings in the visual analysis, the chance for these patients to be treated with intravenous recombinant tissue plasminogen activator may be lost. In order to avoid such situations, it has been shown in our study and other studies that performing quantitative SIR analysis gives more accurate results instead of making decisions with visual analysis only[7,8,13].

In addition, in the studies conducted by Thomalla et al[6] and Song et al[8], the consistency between the observers in the visual analysis was found to be moderate. Although the rate of consistency between observers in our study (κ = 0.627; 95% CI: 0.481-0.772) was found to be slightly higher than in other studies, it is not considered high enough. It is the cases that show a slight increase in hyperintensity that leads to discord among observers. For this reason, quantitative SIR analysis, which is an evaluation method that eliminates subjectivity during lesion analysis, is important in determining the lesion age of the patients who will receive treatment. However, evaluation of these cases with slight hyperintensity only by subjective visual analysis may cause some patients to miss the chance for IV tPA treatment.

In our study, we showed that in addition to the FLAIR SIR value, the DWI SIR value can differentiate the age of the stroke lesion. However, the sensitivity, specificity, and PPV values of the DWI SIR value were lower than those of the FLAIR SIR value. In previous studies, similar results to our study were obtained[4]. Although DWI SIR alone is not as accurate as the FLAIR SIR value, we think that the use of DWI SIR alone in the determination of stroke lesion age can contribute to the treatment of patients whose lesion age is unknown.

There are some limitations in our study; firstly, using the ROI-based method instead of the voxel-based method, which calculates the signal intensity ratio more accurately, limited the more precise evaluation of the SIR value. Secondly, in qualitative analysis, one of our limitations was the subjectivity of evaluating the intensities in the FLAIR sequence as slight, which led to the lack of full agreement between raters. Lastly, one of the shortcomings in our study was also the absence of the penumbra area used for IV tPA treatment and determined by DWI-PWI mismatch. Thus, it may be useful to conduct further studies in which both findings are combined.

Conclusions

In hyperacute ischemic stroke, lesion age can be determined more accurately by quantitative analysis of the SIR value of the FLAIR sequence than by qualitative visual analysis. In patients whose stroke onset time is unknown, the FLAIR SIR value can be used as a biomarker in the treatment of stroke patients within the first 4.5- and 6-hour time windows. Thus, IV tPA treatment can be provided especially in cases that are in the appropriate time window for treatment and show a slight increase in intensity in the FLAIR sequence.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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