# Both ADC and rADC Average Rates in Hyperacute are Lower than those in Acute Stroke

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## Abstract

**Background:** Radiology holds an important role in evaluating patients with suspected stroke. It is therefore important to distinguish hyperacute or acute. DWI-ADC is an important modality. For ADC value measurement, it is more accurate to use multiple b value. There is a significant variability of ADC values in MRI depending on the coil system, imager, vendor, magnetic field strength and multicentre. The purpose of the study is to find out the difference of ADC value in hyperacute and acute stroke. Analytical observational study with cross sectional study approach to determine ADC values differences in Saiful Anwar Hospital Malang. Head MRI of 3T with 3 b values (0, 500, 1000) was performed on every subject. The data were analysed using descriptive statistic.

**Results:** There were 12 subjects observed, 6 in the hyperacute group (onset <24 hours) and acute (onset 24 hours - 1 week). There was a significant difference with $p<0.05$ on average ADC ($10^{-3}$ $mm^2/s$) and rADC (%) values between the hyperacute and acute groups. The ADC average mean ±SD of hyperacute (0.23 ± 0.05) was lower than acute (0.37 ± 0.04), and so as the ±SD rADC mean value of hyperacute (32 ± 8.1) was less than acute (52 ± 4.3).

**Conclusion:** The ADC and rADC average values in the hyperacute were lower than that in the acute group.

***Keywords:*** *DWI, ADC average value, rADC, hyperacute stroke, acute stroke*

## Background

Stroke is a non-traumatic focal vascular abnormality causing injury and permanent damage to the CNS which can be in the form of infarction, ICH, SAH, and is the cause of disability and death worldwide[1,2]. The choice of therapy for stroke depends greatly on the time after the infarct to determine the degree of brain damage [2].

The AAN stated that MRI is better than CT Scan in diagnosing stroke. In the hyperacute phase of CT, a normal picture is often found; whereas DWI MRI can show ischemic lesions[3].

The diffusion coefficient cannot be calculated with DWI, but it can be measured in ADC. The diffusion coefficient can be measured by examining the ADC values reflecting the diffusion speed of water molecules[4]. The cause of ADC current degradation is the theory of cytotoxic oedema[5]. If oedema occurs in cells with a relative change of extracellular volume, it can cause ADC decrease[6].

In a hyperacute, blood flow disruption occurs within minutes, which disturbs metabolism and ion pumps. This results in water movement from the extracellular to the intracellular oedema of the brain; and the diffusion restriction occurs, which results in DWI showing a hypertensive signal along with hypointense in ADC[7]. After ADC decreases, gradual increase occurs due to cell lysis and increased vasogenic oedema in the acute phase[8].

Sasaki *et.al* stated that there is a significant variability of ADC values in MRI depending on the coil system, imager, vendor and magnetic field strength. There is a difference in ADC value of grey and white matter which is about 9% high among vendors, and 4-9% between 1.5T and 3T[9]. There is a difference in ADC values from multicentre and some vendors. To date, there has been

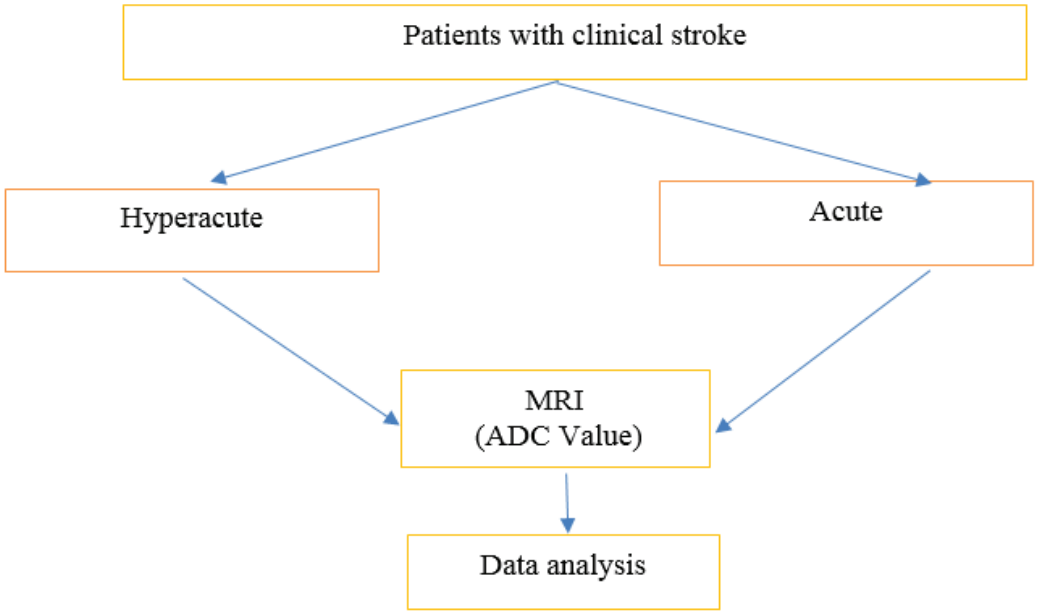
no clinically applicable standard among radiologists[10].

The goal of stroke therapy is to save the penumbra and improve brain function as early as possible[11]. Penumbra is a tissue at risk of infarction, in which perfusion is inadequate for neuronal function but is still sufficient for cell life[12]. Ischemic therapy goes according to ischemic pathogenesis. Therefore, an initial intervention is required to restore blood flow and to protect neurons from ischemic damage. The treatment of ischemic stroke is divided into acute interventions, including endovascular therapy, intravenous rt-PA, and long-term prevention such as risk factor modification, and antithrombotic[13]. There have been no researches on ADC values differences between hyperacute and acute using multiple b values in Indonesian population.

## Methods

This is an analytic observational with cross sectional approach using independent t-test to find out the average value difference of ADC and rADC between hyperacute and acute (. The research was conducted in Saiful Anwar Hospital Malang. The inclusion criteria were patients with stroke with acute and hyperacute onset, whose MRI images showing areas corresponding to the focal neurological deficit. The exclusion criteria were patients with an unclear onset, and with MRI showing a possible picture of multiple sclerosis, tumor or abscess.

This research was conducted with consecutive non-random sampling. Head MRI examination was performed with the following procedures:




The MRI protocol used was as follows: examined by using head coils and sequences including axial SWIp (repetition time [TR] / echo time [TE] 31 ms/ 7.2 ms; field of view (FOV) 23 cm; thickness 2.4 mm; and matrix size 384x255), axial T2 FLAIR (TR / TE 4800/300; FOV 22 cm; thickness 4 mm; and matrix size 278x274), DWI (TR / TE 9449/80; FOV 23 cm; thickness 3 mm; and matrix size 116x114), with b value 0, 500 and 1000 s/ $mm^2$, ADC map was processed with automation based on DWI signal by using formula ADC = ln ($S0/S1$)/($b1$-$b0$) on 2 DWI with b0 = 500 and b1 = 1000.

In the MRI, there was a description of diffusion restriction; were there a T2 shine through picture, the sample was excluded. The ADC values were obtained automatically from DWI using b value b = 0, b = 500, and b = 1000. The ADC value was obtained by placing 4 ROIs in central, pericentral, peri-edge and edge on infarct lesions, with an area of 5 $mm^2$ ROI, outside of the sulcus and ventricle, $mm^2/s$ units with an infarct at least 20 $mm^2$ and then, the ADC average value was calculated. Relative ADC (rADC) was calculated by the

ADC average value on the infarct side / ADC average value on the healthy side x 100%.

The independent sample t-test would be used to analyse the difference of ADC and rADC average values based on infarct age with 95% confidence degree $\alpha = 0.05$, if $p < 0.05$.

## Results

**Table 1. Characteristics**

| | Hyperacute | | Acute | |
|---|---|---|---|---|
| **General** | **Number** | **%** | **Number** | **%** |
| Sex | | | | |
| Male | 5 | 83.3 | 2 | 33.3 |
| Female | 1 | 16.7 | 4 | 66.7 |
| Age | | | | |
| ≤ 50 years | 0 | 0 | 1 | 16.7 |
| 51-60 years | 4 | 66.7 | 2 | 33.3 |
| 61-70 years | 2 | 33.3 | 1 | 16.7 |
| > 70 years | 0 | 0 | 2 | 33.3 |
| Clinical | Number | % | Number | % |
| Diabetes | | | | |
| Yes | 3 | 50 | 1 | 16.7 |
| No | 3 | 50 | 5 | 83.3 |
| Hypertension | | | | |
| Yes | 6 | 100 | 3 | 50 |
| No | 0 | 0 | 3 | 50 |
| Stroke Circulation | | | | |
| Anterior | 5 | 83.3 | 4 | 66.7 |
| Posterior | 1 | 16.7 | 2 | 33.3 |

In this research, ROI of ADC values was taken in 4 areas within the lesion, which were in central (ROI1), pericentral (ROI2), peri-edge (ROI3), and edge (ROI4). The measurement results were read by 2 reviewers. The ADC value obtained from each reader was calculated (ROI1 + ROI2 + ROI3 + ROI4 / 4), so that the ADC average value was obtained. After obtaining the ADC average value, rADC was calculated; in which the formula used was the ADC average / ADC normal value x 100%.

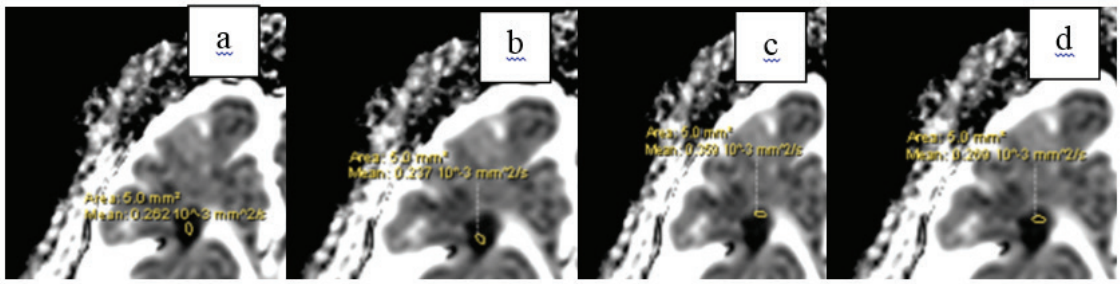



**Figure 1. ROI placement in the infarct areas (a) central, (b) pericentral, (c) edge, (d) peri-edge**

The results show that ADC and rADC average values are lower in the hyperacute group:

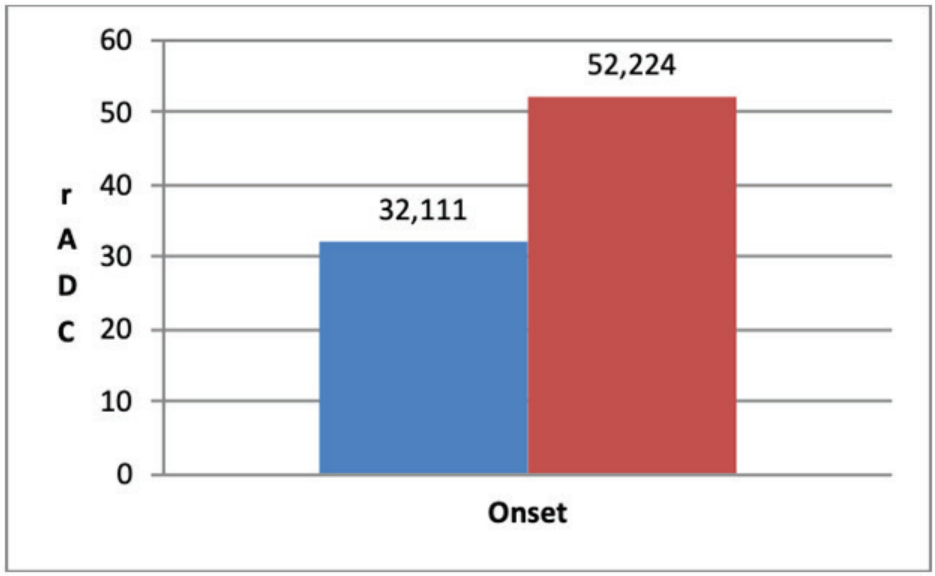



**Figure 2. Chart of ADC average values**

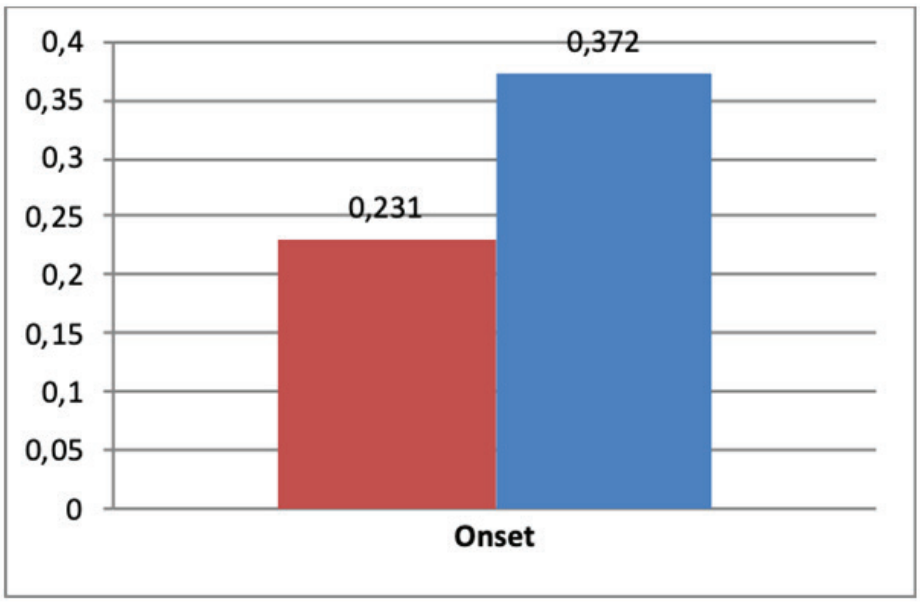



**Figure 3. Chart of rADC average values**

In this research, a significant difference between hyperacute and acute group was found with significance value of p <0.05, in which the hyperacute had lower ADC and rADC average value than the acute group.

**Table 2. T-test results of average ADC and RADC value**

| | | Hyperacute | Acute | t-test Result p value |
|---|---|---|---|---|
| ADC (10-3 mm2/s) | Mean ± SD | 0.23±0.05 | 0.37±0.04 | <0.05 |
| | Median | 0.24 | 0.35 | |
| | Minimum | 0.15 | 0.33 | |
| | Maximum | 0.27 | 0.45 | |
| rADC (%) | Mean ± SD | 32±8.1 | 52±4.3 | <0.05 |
| | Median | 34.5 | 50.9 | |
| | Minimum | 19.0 | 48.1 | |
| | Maximum | 42.1 | 58.6 | |

## Discussion

DWI is an important modality in a stroke case. The ADC can be calculated to quantify the water diffusion on the tissue. ADC is calculated in the intensity of MRI signal that is calculated based on some degree of diffusion using nonlinear regression[16]. This research used 3 b values (0, 500 and 1000) to obtain more accurate ADC value. This is based on a research by Graessner *et.al* that it is minimal to use 3 b values, because it will give more accurate calculation on ADC value. In large b value, for example at b = 1000, Signal Noise Ratio (SNR) is lower so that the standard deviation is higher, but it can be compensated with the median value of b = 500[17].

ADC value is a measurement of fluid molecule diffuses in tissues. The ADC value is influenced by extracellular and cell volume ratio, extracellular composition and temperature[18]. ATP depletion occurs in ischemic tissue, resulting in Na-K ATPase pump trouble and the loss of ionic inter cell membrane gradient. When there is trouble in Na-K ATPase pump, there is water movement from extracellular to intracellular called cytotoxic edema[11]. Cytotoxic oedema causes a decrease in ADC values[8]. This is because at the occurrence of cytotoxic oedema, there is an increase in extracellular volume ratio with cells, so that extracellular diffusion will decrease[18]. In this research, ADC values in each ROI decreased both in hyperacute and acute groups, as compared in the normal parenchyma.

As time goes on, there are changes in DWI and ADC, while it seems that there is no change in conventional MRI and CT. In the acute phase, there is damage to the permeability of blood brain barrier, causing the movement of fluid molecules to move to extracellular; or because of cell membrane damage, intracellular fluid flows out to extracellular[19]. This causes the ADC value to start increasing. This is in accordance with the results of this research. There was a difference in the ADC average value of hyperacute and acute group with p <0.001. The research obtained that the ADC average value of hyperacute group was lower with mean value in the hyperacute group (0.231 ± 0.05) and acute group (0.372 ± 0.04), with a median value of 0.248 in hyperacute and 0.357 in the acute group, minimum 0.15 and maximum 0.27 in the hyperacute group and 0.33,

0.27 in the acute group.

The main purpose of this research was to look at the comparison of ADC values in hyperacute and acute groups. If measurements were made on only one ROI, it would not represent a value yet. In this research, the measurement was done by using 4 ROI areas, namely central, pericentral, edge and peri-edge, assuming the perception among radiologists is the same. Shen *et.al* stated that the increase of ADC values in stroke from central to peripheral might be due to degrees of damage[19]. In this situation, there will be differences in ADC values in the central and peripheral areas. Therefore, the researchers used the ADC average value in the four areas mentioned earlier.

One of the factors influencing ADC value is the width of the ROI. A research conducted by Bilgili *et.al* stated that there is a significant variation of ADC values in the brain between the two observers, with different ROI areas[21]. To reduce this variation, this research used the area of 5 $mm^2$ to make it standardized.

The normal value of ADC does not change significantly with age. There is no significant difference between men and women, or between hemispheres[22]. In order to obtain normalized ADC values and to reduce differences among individuals, this research used a normal ADC value in the contralateral parenchyma that is the same lesion anatomic point with the infarct area to measure the relative ADC, which is comparing the ADC average value with a normal ADC value multiplied by 100%. rADC is better and may reduce the bias compared to ADC values for evaluation of diffusion abnormalities [9].

In this research, there were different rADC values in the hyperacute and acute groups by using independent t-test. The significance value was $p < 0.05$. The data showed a higher rADC value in the acute group, with mean $52 \pm 4.3$ and lower in the hyperacute group of $32 \pm 8.1$, with median of 50.9 in the acute group, and 34.5 in the hyperacute group.

The main therapy of ischemic stroke is to improve blood flow so as to reduce brain tissue damage by saving the penumbra area[13]. Until recently, the one approved by the FDA is thrombolytics using rtPA which is only for the limited patient[11]. If reperfusion is performed over a window period, the risks of bleeding will increase[23]. The mechanism of cerebral hemorrhage as an ischemic complication is a phenomenon known as reperfusion injury. Reperfusion injury causes several inflammatory responses resulting in endothelial cell damage causing blood brain barrier damage, oedema and haemorrhagic transformation[24]. In this research, the ADC and rADC average value were higher in the hyperacute group, this indicates that there is already blood brain barrier damage so that it causes vasogenic oedema leading to the change of ADC value.

This is a preliminary research. Although there is a statistically significant difference in ADC and rADC average values, in which ADC values are lower in the hyperacute phase, it cannot represent the cut off value of ADC yet. Therefore, further research by using a larger population is required. MRI examination, particularly DWI-ADC on hyperacute and acute strokes, can assist in the diagnosis of stroke and provide additional information as a consideration for therapy.

## Conclusion

There is a significant difference in ADC and rADC average value in hyperacute and acute stroke, in which the average value of hyperacute is lower than that of acute.

It is necessary to conduct a further study by using larger population so that the cut off value difference of ADC and rADC can be determined.

The authors declare that they have no competing of interests.

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