European Journal of Medical and Health Sciences
www.ejmed.org

Correlation between the Volume of MRI Brain Infarct and Inflammatory Markers among Acute Ischemic Stroke Patients

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ABSTRACT

Stroke is one of the top five leading causes of death in Malaysia and increases in the mortality rate between 2016 and 2019. There is growing evidence that inflammation plays an important role in acute ischemic stroke. Studies showed that the level of inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are strongly correlated with the volume of brain infarct detected using Magnetic Resonance Imaging (MRI). This cross-sectional study conducted in Hospital Pengajar Universiti Putra Malaysia (HPUPM) aims to determine the correlation between the volume of MRI brain infarct with inflammatory markers among patients with acute ischemic stroke in HPUPM. Patients' sociodemographic information and level of inflammatory markers were extracted from the Hospital Information System (eHIS), the MRI images were accessed through the Picture Archiving and Communication System (PACS) whereas the MRI reports for each sample were searched from the Reporting Information System (RIS). In addition, the MRI sequences DWI/ADC and FLAIR axial were selected. The findings of the site and size of brain ischemia were studied. This study was based on 60 data sets of patients diagnosed with acute ischemic stroke in HPUPM. The majority of the patients were male (68.3%), Malay (51.7%) and ranging from age group 61-75 years old. The mean volume of MRI brain infarction was 27.3268±55.6957cm^3. A statistically significant association was found between CRP and volume of brain infarction ($r=0.297$, $p<0.05$) whereas no association was found between ESR and volume of brain infarction ($r=0.192$, $p>0.05$). A significant association was found between CRP and volume of brain infarction. No association was found between ESR and volume of brain infarction.

Keywords: Acute ischemic stroke, an inflammatory marker, MRI, volume brain infarct.

Submitted : June 5, 2023

Published : August 31, 2023

ISSN: 2593-8339

DOI: 10.24018/ejmed.2023.5.4.1845

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I. Introduction

According to the World Health Organization (WHO), stroke is the second major cause of death involving almost seven million deaths in 2012 worldwide [1]. In Malaysia, stroke is one of the top five leading causes of death and there was also an increase in the overall stroke mortality rate between 2016 and 2019 [2]. Several inflammatory markers are commonly used in primary care for diagnosis and monitoring the inflammatory condition including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and plasma viscosity. Increased CRP level was noted to be associated with the prothrombotic condition and increased platelet activity. Dahshan *et al*. stated that levels of CRP correlated with the severity that is measured using NIH Stroke Scale/Score (NIHSS) and infarction size at the onset. Other than that, fibrinogen is increased during acute-phase reaction, therefore, ESR increases too [3]. Kisialiou *et al*. conducted a study that observed the values of ESR as soon after the insult and found higher levels of ESR indicates larger infarct size with long-term poor outcome [4]. MRI protocols such as DWI stroke volume, infarct core volume, and DWI aspects systems that measure the infarct volume in acute ischemic stroke showed high inter-reader reliability and good prediction power for clinical outcomes and appeared to be superior to CT ASPECTS systems [2], [5].

This research aims to evaluate the correlation between the volume of MRI brain infarct with the inflammatory markers (CRP and ESR) among acute stroke ischemic patients. The findings are hoped to deepen the understanding on how these inflammatory markers play an important role in determining the prognosis of the patients and may be affected by demographic factors and risk factors. Lastly, it is hoped that this study will serve as a useful guide to the doctors out there in helping to determine the diagnosis and prognosis of acute ischemic stroke patients in Malaysia.

II. Material and Methods

A. Type of Study

This study was conducted in Hospital Pengajar Universiti

Putra Malaysia, which is located in Serdang, Selangor, near Putrajaya. It is planned to serve approximately 570 000 population in Serdang, Putrajaya, Kajang and Bangi. The hospital which occupies 400 beds serves as a teaching hospital for students from University Putra Malaysia. It has commenced its operation in March 2019.

Inclusion criteria:

a. Age >18 years old.

b. All patients with acute ischemic stroke.

c. MRI brain done <24 hours from onset of stroke in HPUPM between January 2020 until February 2021.

Exclusion criteria:

a. Pregnant patient.

b. Patient with ischemic stroke >24 hours.

c. Trauma patients.

d. Patients who have a history of previous brain surgery.

e. Patients with intracranial bleed, venous sinus thrombosis, infection, or underlying malignancy.

B. Study Design

This was a cross-sectional study using primary data, in which the data was obtained from patients who came to Res Q (Stroke Center) in HPUPM and research purposes which is within inclusion criteria.

C. Study Duration

The study duration was one year which starts from January 2021 until December 2021. The data collection was taken from January 2020 until December 2022.

D. Sampling

The study population are all patients with acute ischemic stroke who went for MRI brain examination. The lists of patients who went for MRI brain examination retrieved from the PACS and Radiology Information system (RIS). The sociodemographic and clinical assessment of the patients were assessed via the Hospital Information System (eHIS). The sampling unit is a patient from HPUPM who met the inclusion and exclusion criteria, underwent MRI brain examination within the period of January 2020 until December 2022.

The sample size (n) for this study was calculated using the formula:

$$P = \frac{P_1 + P_2}{2} = 0.097$$

$$n = \frac{\left\{\left[Z_{(1-\alpha/2)}\sqrt{2\bar{P}\left(1-\bar{P}\right)}\right] + \left[Z_{(1-\beta)}\sqrt{P_1\left(1-P_1\right) + P_2\left(1-P_2\right)}\right]\right\}^2}{\left(P_1 - P_2\right)^2}$$

where

P_1 – Most significant outcome of ischemic stroke in 2014 (NIHSS 5-20) = 0.482

P_2 – Least significant outcome of ischemic stroke in 2014 (NIHSS >21) = 0.171

$Z_{(1-\alpha/2)}$=1.96 for 95% CI;

$Z_{(1-\beta)}$ = power = 80%= 0.84.

Therefore, the sample size obtained is n=30 subjects per group × 2 groups, = 60 subjects (Total subjects in this study).

An additional adjustment was made, and the final sample size is 72 subjects.

P1: Group of patients that experienced a moderate neurological deficit.

P2: Group of patients that experienced a severe neurological deficit.

E. Study Instrument and Data Collection Technique

The sociodemographic data and level of CRP and ESR of patients which fulfilled the study criteria were retrieved from the Hospital Information System (eHIS) while the MRI images were accessed via Picture Archiving and Communication System (PACS) whereas the MRI reports for each sample were searched from the Reporting Information System (RIS).

MRI sequences DWI/ADC and FLAIR axial were selected and reference for techniques of measurement is taken from the previous study by [3] (Fig. 1). The measurements were done by two investigators and taken three times and average figures were taken to reduce bias measurement. All the data were recorded in the study pro-forma.

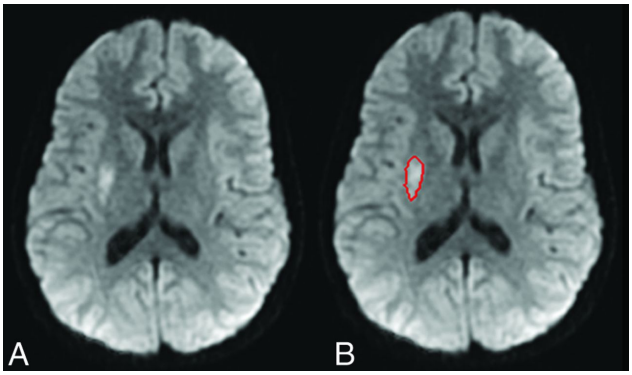

Fig. 1. (A) Reduced diffusivity within the right putamen consistent with an area of acute infarction. (B) the contour derived from the semi-automated computer segment mentation software that is used to derive infarct volume [16].

Segmentation was performed by manual tracing of regions of reduced diffusion on DWI sequences. All manual segmentations were performed at a dedicated workstation.

F. Ethical Considerations

Ethical approval for this study will obtain from Ethics Committee for Research Involving Human Subjects Universiti Putra Malaysia or Jawatankuasa Etika Universiti untuk Penyelidikan Melibatkan Manusia (JKEUPM).

All data and information gathered from this study are kept and handled in a confidential manner that has followed the applicable laws and regulations. All the data collected would be kept for a minimum of three years for data analysis and after that, all of it would be destroyed.

III. Results

Among 60 acute ischemic stroke patients in HPUPM, there were 41 (68.3%) males and 19 (31.7%) female patients. From 60 patients, 21 (35%) of them were in the age group of 61-75 years old and majority of them were Malay with 51.7%.

A. Medical History

Table I showing, hypertensive patient recorded the highest frequency which is 43 patients (71.7%), followed by

hyperlipodemia in 33 patients (55%). 5 AIS patients (8.3%) are having ischemic heart disease. 29 patients (48.3%) have underlying diabetes mellitus.

TABLE I: MEDICAL HISTORY

Medical history	Frequency (n)	Percentage (%)
Hyperlipidaemia	2	3.3
IHD	5	8.3
DM	30	50
Dyslipidaemia	30	50
Hypertension	44	73.3

B. Inflammatory Markers in Acute Ischemic Stroke Patient

As shown in Table II, CRP levels were reported in 57 of the patients whereas ESR levels were reported in 28 of the patients. CRP levels have a mean of 42.85±42.1436 mg/dl and a median of 19 mg/dl with IQR of 60.5 mg/dl as well as positively skewed (non-normal distribution). ESR levels has a mean of 32.321±33.1618 mm/h and a median of 24.5 mm/h with IQR of 36.0 mm/h as well as positively skewed (non-normal distribution).

TABLE II: CRP AND ESR LEVELS IN ACUTE ISCHEMIC STROKE (AIS) PATIENTS

	CRP (mg/dl)	ESR (mm/h)
n	57	28
Minimum	0.5	3.0
Maximum	207.8	120.0
Mean	42.85±42.1436	33.231±33.1618
Median	19.0	24.5
Interquartile range	60.5 (6.15-66.65)	36.(5.0±41.0)
Skewness	1.765	1.531

C. Site of Brain Infarct

Table III showing 23 (38.3%) patients had a middle cerebral artery (MCA) infarction, 19 (31.7%) had a lacunar infarction, 4 (6.7%) had a Posterior cerebral artery (PCA) infarction and 2 (3.3%) had an Anterior cerebral artery (ACA) infarction. Watershed or borderzone infarcts occurred in 3 (5.0%) patients. Infarctions affecting the precentral or postcentral gyrus supplied by the ACA and MCA occurred in 3 (5.0%) (Fig. 2), whereas cerebellar infarction also occurred in 4 (6.7%) patients. In 2 (3.3%) patients, the infarction site was not specified.

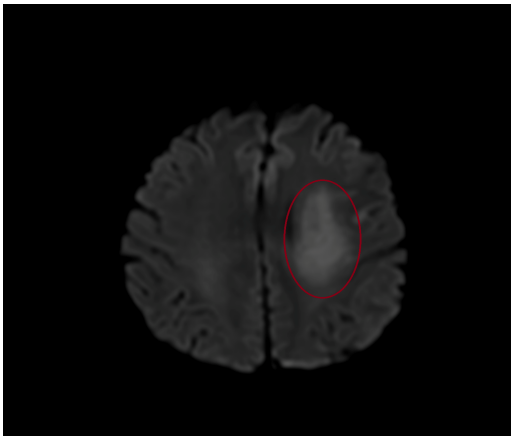

Fig. 2. MRI-DWI of AIS patient with left MCA infarction. Hyperintense areas (red circle) are denoted as infarctions.

TABLE IIII: SITE OF BRAIN INFARCT

Infarct Site	Frequency	Percentage (%)
MCA infarct	23	37.3
Lacunar infarct	19	31.7
PCA infarct	4	6.7
ACA infarct	2	3.3
Watershed infarct	3	5.0
Pre/Postcentral Gyrus infarct	3	5.0
Cerebellar infarct	4	6.7
Unspecified	2	3.3

D. Volume of Brain Infarct

The volume of infarction measured from the 60 total patients using MRI-DWI ranged between 0.06 cm^3 and 323.57 cm^3 with a mean of 27.3268±55.6957 cm^3 and a median of 6.1350 cm^3 (Fig. 3). The data was significantly skewed to the right with significant kurtosis indicating non-normal distribution (Table IV).

TABLE IV: VOLUME OF BRAIN INFARCT (CM^3)

	Volume of brain infarct ($cm^{3)}$
Minimum	0.06
Maximum	323.57
Mean	27.9268
Median	6.1350
Standard deviation	56.6957
Skewness	3.413
Kurtosis	13.986

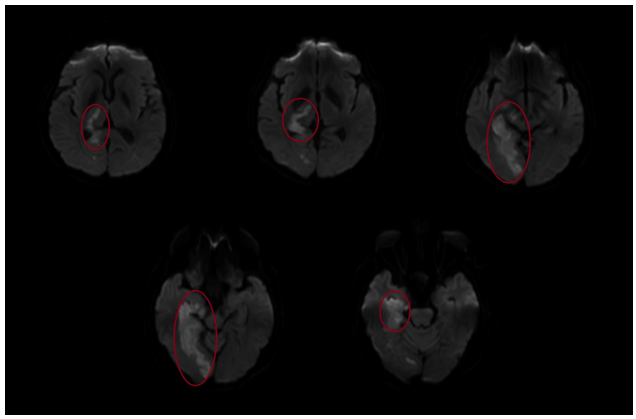

Fig. 3. MRI-DWI of AIS patient with left MCA infarction. Hyperintense areas (red circle) are denoted as infarctions.

E. Association between Demographic Factors and Inflammatory Markers

Table V demonstrates the associations between CRP and demographic factors. The association between CRP and age was tested using the Spearman correlation test and resulted in a correlation coefficient of rs=0.133 and a p-value of 0.328 indicating no statistical association. Correlation between CRP and gender was tested using the Mann Whitney U test and resulted in U=339.5 and p-value=0.843 indicating no correlation. Lastly, an association between CRP and race was tested using the Kruskal Wallis H test and resulting in H(2)=4.955 and p-value=0.084 indicating a non-statistically significant association.

TABLE V: CORRELATION BETWEEN CRP AND DEMOGRAPHIC FACTORS

Correlation coefficients		P-value
CRP-Age	rs = 0.133	0.328
CRP-Gender	U = 339.5	0.843
CRP-Race	H(2) = 4.955	0.084

Table VI demonstrates the associations between ESR and demographic factors. The association between ESR and age

was tested using the Spearman correlation test and resulted in a correlation coefficient of rs=0.354 and p-value=0.64 indicating no statistical association. Correlation between ESR and gender was tested using the Mann Whitney U test and resulted in U=31.5 and p-value=0.116 indicating no correlation. Lastly, the association between ESR and race was tested using the Kruskal Wallis H test and resulting in H(2)=1.088 and p-value=0.580 indicating no association.

TABLE VI: CORRELATION BETWEEN ESR AND DEMOGRAPHIC FACTORS

Correlation coefficients		P-value
ESR – Age	rs = 0.354	0.640
ESR – Gender	U = 31.5	0.116
ESR – Race	H (2) = 1.088	0.580

F. Association between Inflammatory Markers and Volume of MRI brain infarct

Table VII demonstrates the correlation between inflammatory markers and volume of MRI brain infarct. The patients with recorded CRP values (n=57) were tested for association of CRP and volume of infarction. The Spearman's Correlation test was used. There is a weak correlation between CRP level and volume of MRI brain infarct with r=0.297. This correlation between CRP level and volume of MRI brain is statistically significant with p-value=0.025 which is less than the significant value ($p<0.05$). The patients with recorded ESR values (n=28) were tested for association of ESR and volume of infarction. The Spearman's Correlation test was used. There is a negligible correlation between ESR level and volume of MRI brain infarct with r=0.192. This correlation between ESR level and volume of MRI brain is not statistically significant with p=0.326 which is larger than the significant value ($p<0.05$)

TABLE VII: CORRELATION BETWEEN INFLAMMATORY MARKERS AND VOLUME OF MRI BRAIN INFARCT

			CRP level (mg/l)	ERS level (mm/h)
Spearman's rho	Infarct volume	Correlation coefficient	0.297	0.192
		Sig. (2-tailed)	0.025*	0.0326
		N	57	28

IV. DISCUSSION

A. Association between Demographic Factors and Inflammatory Markers

The current study shows that there was no association between the demographic factors (age, gender and race) and the CRP levels. Spearman's correlation showed there was no association between CRP levels and age in patients with acute ischemic stroke with (r=0.133, p=0.328). This result contradicts the findings by Paczek *et al*. which shows that ageing is associated with a state of chronic low-grade inflammation and increased serum levels of inflammatory markers which includes the CRP levels [6]. These contradicting findings may be contributed by the small sample size of acute ischemic stroke patients treated in HPUPM during the study duration. Mann Whitney U test showed U=339.5 and p-value=0.843 which indicates no association between CRP levels and gender of patients with acute ischemic stroke. In our study, the majority of patients with acute ischemic were male (68.3%) and the rest were females (31.7%). According to a study by Khera *et al*. [7], significant race and gender differences exist in the population distribution of CRP. The results in our study and the study conducted by Khera *et al*. [7] contradicts because of the location of where our study was conducted which was in HPUPM only and thus the result cannot be used to determine the association between CRP levels and gender of patients as a study supposed to include more locations [7]. Kruskal Wallis H test which showed H(2)=4.955 and p-value=0.084 indicates there was no association between CRP levels and race of patients with acute ischemic stroke. In our study, the majority of the patients were Malays (51.7%), followed by Chinese (25%) and Indians (23.3%). A study conducted by Nazmi *et al*. states that race or ethnicity was independently associated with CRP levels of African, Latin, or South Asian descent were at higher risk for elevated CRP than subjects of European descent [8]. However, the results in our study show there is no association and this may be due to the fact that our study only compares the race among Malaysians and no other ethnicities.

The current study also shows that there was no association between demographic factors (age, gender, and race) and ESR levels. Spearman's correlation test showed there was no association between ESR levels and age in patients with acute ischemic stroke with (r=0.354, p=0.640). Mann Whitney U test was used for ESR levels and gender in patients with acute ischemic stroke and showed no association with U=31.5 and p-value=0.116. Kruskal Wallis H test showed no association between ESR levels and race of patients with acute ischemic stroke with H(2)=1.088 and p-value=0.580. There is no significant association of demographic factors and ESR levels as well since this study has many disadvantages of not being able to get a large sample size, a proper location of the study and slight biases in choosing patients. Most of the studies that were done to measure the inflammatory markers with the demographic factors have shown significant results or unclear results, thus this study proves to be insufficient to determine the association between these variables [9].

B. Association between Inflammatory Markers and Volume of MRI Brain Infarct

Spearman correlation test showed a weak correlation between CRP levels and volume of brain infarct in acute ischemic acute stroke patients in HPUPM which is statistically significant (r=0.297, p-value=0.025). These findings are similar to a study by Youn *et al.* in which they described an association between CRP levels and the volume of brain infarct (r=0.239, p-value=0.010) [10]. These findings also offer a slight contrast to the results found by Heidi *et al*. in which they found a moderate correlation between CRP and volume of brain infarct (r=0.47, p-value=0.005) [11]. Moreover, CRP level and volume of infarct are both individually correlated with the severity of stroke [7], [8]. CRP plays an important role in the human immune system. Since CRP is a marker for inflammation, this shows that inflammation may play a significant role in acute ischemic stroke. From these findings, it can be concluded that levels of CRP may be correlated with volumes of brain infarctions, however in what way and to what extent is not yet clear.

Spearman's Correlation test in this study showed there was

a negligible correlation between ESR level and the volume of MRI brain infarct (r=0.192, p-value=0.326) This result is similar to the findings by Comoglu *et al*., in which this study revealed that ESR level is not specific enough to predict the prognosis of patients with acute ischemic stroke [12]. However, many researchers found that there is a correlation between ESR level and the volume of MRI brain infarct. As an example, Kisialiou *et al*. reported that a high ESR value is associated with larger infarct size [4]. Similarly, a study done by Nayak *et al*. [13] found that higher ESR in the acute phase of a stroke may indicate a greater increase in fibrinogen concentration and a more significant reduction in cerebral blood flow which revealed a higher volume of brain infarct. This contrast finding might relate to the fact that ESR is a nonspecific marker of infection and inflammation [14]. Other than that, ESR is an indirect method to reveal the red blood cell aggregation. Another possible reason ESR level cannot be used to determine the volume of brain infarct in our study may be related to the timing of ESR measurement. This study was focused on ESR level during admission, and this might be more informative if the serial measurement were performed for the consecutive peak value following the insult.

V. Conclusion

The majority of the patients in our study were male, Malay and ranging from age group 61-75 years old. Most underlying medical conditions recorded among the patients are hypertension, hyperlipidemia and diabetes mellitus. Patients were mostly admitted with high levels of CRP, but the majority recorded normal ESR levels. MCA infarction was the most common affected area. There was no association between demographic factors (age, gender, and race) with inflammatory markers (CRP and ESR levels) in acute ischemic stroke patients in this study. Statistically significant association was found between CRP and volume of brain infarction whereas no association was found between ESR and volume of brain infarction.

VI. Recommendation

Based on our study, some recommendations can be suggested to both clinicians and researchers:

1. CRP levels may be used as a general indicator of the extent of brain infarction in acute ischemic stroke patients.
2. Further research regarding the association between the volume of infarction and inflammatory markers that involves larger sample sizes with longer duration may improve accuracy and may present more significant and accurate results.
3. Studies exploring the significance and the association of volume of infarction with other relevant laboratory markers in ischemic stroke patients may help further our understanding on this matter.

Acknowledgment

We would also like to show our deepest gratitude towards the patients who participated in this research, authorities of Universiti Putra Malaysia (UPM) who provided us with the official approval for this study and lastly, to our family and friends for the continuous support and encouragement.

Conflict of Interest

Authors declare that they do not have any conflict of interest.

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