The Diagnostic Potential of Glial Fibrillary Acidic Protein (GFAP) in Acute Stroke Patients

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Abstract:

Background: Ischaemic stroke (IS) and hemorrhagic stroke (HS) are considered second leading cause of death and causing great disability. Neuroimaging techniques are primarily used to differentiate between them; however, they are not available in all centers and cannot be used in some patient.

Aim: Identifying blood biomarkers that could be easily measured and could differentiate between IS and HS.

Method: This study was case control study; it was performed on 75 subjects: 50 stroke patients and 25 control subjects. Blood samples collected within 24 hours of stroke symptoms. GFAP, IL6, CRP was measured by ELISA technique.

Result: This study found that GFAP is significantly higher in stroke patient compared to control group ($p < 0.0001$). However, no significant difference was observed between IS and HS. In addition, IS and HS showed significantly higher IL-6 levels compared to control ($p < 0.0001$). Also, it was demonstrated highly significant differences in CRP levels among the groups ($p < 0.0001$). The area under curve of GFAP for discriminating between IS and HS patients were 0.7385, using a cut-off point of (≥235.26pg/ml) GFAP was able to differentiate between IS and HS with 84.62% and 73.08% sensitivity and specificity, respectively. It was demonstrated that there was no correlation between GFAP and IL6 and CRP.

Conclusion: GFAP has acceptable differentiation ability to differentiate between IS and HS

Keywords: ischemic stroke, hemorrhage stroke, biomarkers, GFAP, inflammatory markers.

الإمكانات التشخيصية للبروتين الحمضي الليفي الدبقي (GFAP) لدى مرضى السكتة الدماغية الحادة

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الخلاصة:

الخلفية: تُعتبر السكتة الدماغية الإقفارية (IS) والسكتة الدماغية النزفية (HS)ثاني أكثر أسباب الوفاة شيوعًا، وتُسبب إعاقة بالغة. تُستخدم تقنيات التصوير العصبي بشكل أساسي للتمييز بينهما، إلا أنها غير متوفرة في جميع المراكز، ولا يُمكن استخدامها لدى بعض المرضى.

الهدف: تحديد المؤشرات الحيوية في الدم التي يُمكن قياسها بسهولة، والتي تُمكن من التفريق بين IS وHS

المنهجية: أُجريت هذه الدراسة كدراسة حالة وشاهد، على 75شخصا: 50 مريضًا بالسكتة الدماغية و25 شخصا في المجموعة الضابطة. جُمعت عينات الدم خلال 24 ساعة من ظهور أعراض السكتة الدماغية. قُيست مستويات GFAP، وIL6، وCRP باستخدام تقنية ELISA.

النتيجة: وجدت هذه الدراسة أن GFAP أعلى بشكل ملحوظ لدى مرضى السكتة الدماغية مُقارنةً بالمجموعة الضابطة (p <0.0001). ومع ذلك، لم يُلاحظ أي فرق معنوي بين IS و HS.بالإضافة إلى ذلك، أظهرت IS وHS مستويات IL-6 أعلى بشكل ملحوظ مُقارنةً بالمجموعة الضابطة. (p < 0.0001) كما ثبت وجود فروق ذات دلالة إحصائية عالية في مستويات البروتين التفاعلي سي (CRP)بين المجموعات (p < 0.0001). بلغت AUC لGFAPللتمييز بين مرضى IS و 0.7385 HS، باستخدام نقطة حدية (≤ 235.26 بيكوغرام/مل). وقد تمكن GFAP من التمييز بين IS وHS بحساسية وخصوصية 84.62% و73.08% على التوالي. وقد ثبت عدم وجود ارتباط بين GFAP وIL6 وCRP .

الخلاصة: يتمتع GFAP بقدرة تمييز مقبولة بين السكتة الدماغية الإقفارية والسكتة الدماغية النزفية

الكلمات المفتاحية :السكتة الدماغية الإقفارية, السكتة الدماغية النزفية، العلامات الحيوية، البروتين الحمضي الليفي الدبقي (GFAP)، علامات الالتهاب

Introduction:

Stroke is known as a neurological impairment, there are mainly three types of it: ischaemic, intracerebral hemorrhage (ICH), and subarachnoid hemorrhage (1).Yearly, stroke occur in about twelve million people globally, and cause death of more than 5.5 million individual yearly in the last two decades. Stroke is cosidered second leading cause of death and cause long lasting disability in about 5 million of subjects, in 2019 in Iraq stroke occurrence rate was ranged from 196.2 to 218.3 per 100,000 people(2). 80% of stroke cases are ischemic stroke(IS) while hemorrhagic cases affect approximately 20% of total(3). Patients may present with facial droop, arm weakness or slurred speech. The patients may suffer dysphagia, vertigo, **and/or** visual disturbance. Patients with stroke can be present with any of previuosly mentioned symptoms not all of them and they are helpful in diagnosis of stroke(4). Patients with hemorrhagic stroke may have sudden severe headache, vomiting and neck pain and nuchal rigidity (stiffness) may also occur(5). Ischaemic stroke is caused by blockage of blood supply to certain area in the brain this blockage may be due to atherosclerosis that occur in large artery or due to an embolus. while hemorrhagic stroke occurs when there is ruptur of certain cerebral blood vessel therefore the blood will accumulate inside the brain and in this case it will called intracerebral hemorrhage, or the rupture occur at surface of brain and the blood accumulate in subarachnoid space, called SAH(6). Stroke have non modifiable risk factors for example age, family history and sex. Stroke also have preventable risk factors such as hypertension, cigarette smoking, diabetes, alcohol drinking, sedentery life style and atrial fibrillation(7). Neuroimaging such as computed tomography (CT) scan and magnetic resonance image (MRI) is required to differentiate between ischaemic stroke and intracerebral hemorrhage (8). These techniques have number of problems for example, magnetic resonance image (MRI) is known to have higher sensitivity than other methods for identification of acute ischaemic stroke(AIS). However, MRI is not widely available in all hospitals and it is less accessible than CT, moreover it is mainly employed for follow up purposes. In addition, MRI require longer imaging times(9). Furthermore, CT images are often normal in early hours after symptoms and access to CT perfusion and MRI is difficult and it is not available in all centers and since the treatment of acute ischaemic stroke (AIS) is time dependent (within 4.5 hour of symptom) and till now there is no specific

marker for it in blood(10). Early diagnosis and treatment of stroke is critical as early intervention can prevent long-term disability and minimize the risk of complications and this lead improve patient functional outcome (11). So aim of this study to find serum biomarker that can be easily measured and could differentiate between ischaemic and hemorrhagic stroke. Glial fibrillary acidic protein (GFAP), a class III intermediate filament protein, found mainly in astrocytes in central nerves system. GFAP is important to maintain structure and shape of astrocytes(12). Astrocytes have many essential functions in both healthy and **The aim of the study**: The aim of the study was to investigate the diagnostic ability of GFAP for ruling out intracranial hemorrhage

Method:

This study was done on 50 patients suffering from stroke at AL-Yarmook Teaching Hospital in Baghdad, Iraq and control subjects (number=25) who did not have stroke or history of stroke. However, some of these subjects had risk factors of stroke for example hypertension, diabetes, dyslipidemia or other risk factors to ensure consistency of result, at the period from October 2024 to March 2025. The blood samples were taken from participants during 24 hour after onset of symptoms to determine levels of GFAP, CRP and IL6. About 4-5 ml of venous blood samples were collected from each patient and put it in gel tubes then after about 30 minute and not longer than 1 hour, the blood samples were centrifuged at 4100 rpm for 8 minutes to get serum, then serum was divided into eppendorf tubes and stored at –20 c^0 till the time of analysis. All patients were diagnosed by neurologists and determine if the patient had ischaemic stroke or hemorrhagic stroke. All participants were asked to fill informed consents for the participation in the study and the study was ethically approved by the local ethical committee of the College of Pharmacy/Mustansiriyah University.

Inclusion criteria:

injured brain(13). Astrocytes are one of the cell type that present in the blood brain barrier (14). In event of intracerebral hemorrhage, disruption of astrocyte lead to rapid release of glial fibrillary acidic protein in the bloodstream, whereas in case of acute ischaemic stroke, GFAP is released more slowly. According to systematic review and meta-analysis GFAP is considered a promising diagnostic biomarker for early detection and diagnosis of intracerebral hemorrhage (15). Therefore the GFAP may be utilized as a potential biomarker to distinguish between hemorrhagic and ischaemic stroke(16).

in a case control study in Iraqi stroke patients and to explore its correlation with inflammatory markers.

All patient ≥18years old with acute stroke who presented within 24 hours.

Exclusion criteria:

Patients with autoimmune disease, infection, tumour, head trauma, intracranial tumors and neurodegenerative diseases.

Design of the study:

The design of the currrent study was a case-control study. Participants divided into three groups: ischaemic stroke (IS) group (number=25), hemorrhagic stroke (HS) group (number=25) and control group (number=25).

Reagent and kits

Human GFAP (Glial Fibrillary Acidic Protein) ELISA Kit was used to determine concentration of GFAP. Human IL-6(Interleukin 6) ELISA Kit (E-EL-H6156) and Human CRP(C-Reactive Protein) ELISA Kit (Elabscience, China), was used to determine concentration of IL-6 and C reactive protein, respectively(17). The reference range of IL-6 was 0–16.4pg/mL(18). Meta anslysis found that for IL-6 in the blood of healthy donors range from 0 to 43.5 pg/ml(19).

Statistical analysis

All statistical analyses were performed using GraphPad Prism version 10.5. Shapiro–Wilk test was used to assess normality

distribution of data. Depending on data distribution, either ANOVA or Kruskal–Wallis tests were used for groups comparisons, with appropriate post hoc analysis. Mann whitney test and t test was used as appropriate. Categorical data were analyzed using either Chi square or Fisher's exact test. ROC curve analysis was used to assess diagnostic performance. A p-value < 0.05 was considered statistically significant.

Result:

Demographic distribution and the clinical characteristics of the patients and the control groups:

Fifty patients with acute stroke and 25 control subjects were included into the study. Among these, 25 were IS and 25 patients had hemorrhagic stroke. Baseline variables are presented in Table 1. The mean age control group was 54.04±9.93 and IS patients was 66.92±12.11 years and hemorrhagic stroke was 52.20±11.53 years with significant difference between the age distribution among the study groups where (*P* <0.0001). The present study found there was no significant difference in BMI across the three groups (p = 0.4705). In this study, there were 52% male among control group, 92% males among IS and 76% among hemorrhagic patients with statistically significant differences in sex proportions across groups (p= 0.0056). In the current study, there was significant difference in the prevalence of smokers among the study groups (p =0.004), in which HS patients had the highest proportion compared to control and IS. Regarding hypertension, this research investigated highly significant differences in hypertension prevalence among the groups (p < 0.0001), in which IS patients (100%) and HS (92%) have the highest prevalence of hypertension compared to control group which had the lowest prevalance (56%) of hypertension. In addition, in the present study it was found significant differences in diabetes prevalence across groups (p = 0.0155), with highest prevalence in IS (60%) and HS (40%) patients. Also, this study revealed significant differences with regard to previous history of stroke across groups (p <0.001), with highest percentage in IS (48%). Median time of taking the blood after symptom onset was 12hours (1-24hour), 11.5hours (1-24) in IS and HS, respectively

Table 1. Demographic distribution data and the clinical characteristics of the patients and the control group

Characteristics	Control(n=25)	IS (n=25)	HS (n=25)	*P*-value
Age(years)	54.04 a ± 9.93	66.92 b ± 12.11	52.20 a ± 11.53	*0.001
BMI(kg/m^2)	29.30 a (25.99-35.57)	27.68 a (24.74-32.05)	30.07 a (25.54-33.51)	**>0.05
Sex Male(%)	52%(13/12)	92%(23/2)	76%(19/6)	0.0056
Smoking % Yes/no	12% (3/22)	44%(11/14)	56%(14/11)	0.004
HTN % Yes/no	56%(14/11)	100%(25/0)	92%(23/2)	<0.001
DM % Yes/no	20% (5/20)	60% (15/10)	40% (10/15)	0.0155
Previous stroke% Yes/no	0%(0/25)	48%(12/13)	32% (8/17)	<0.001
Time of taking the blood after symptom onset median(range)	-	11.5hour (1-24)	12hour (1-24hour)	-

*The data were expressed as Mean ± SD; **data were expressed as median(interqurtile range); p value < 0.05 is considered as statistically significant;mean or median followed by the same letter are not significantly difference while,mean or median followed by different letters are significantly different; IS: ischaemic stroke; HS: hemorrhagic stroke; BMI: body Mass Index; n: number; % percentage; SD: standard deviation; DM: diabetes mellitus; HTN:hypertension.

Serum levels of Glial fibrillary acidic protein, Interleukin 6 and C-reactive protein in the patients and the control groups:

In the present study, it was found that there was significant difference in GFAP levels ($p < 0.0001$) among the groups. Control exhibited markedly lower levels versus IS ($p < 0.0001$) and HS ($p < 0.0001$). Critically, no significant-difference was noticed between IS and HS ($p = 0.148$), as shown in Table 2 and Figure 1. On the other hand, the current study revealed highly significant differences in IL-6 levels ($p < 0.0001$). Control exhibited significantly lower IL-6 level compared to IS ($p < 0.0001$) and HS ($p < 0.0001$). However, no significant difference was observed between IS and HS ($p = 0.2327$), as illustrated in Table 2 and Figure 2. Also this study demonstrated highly significant differences in CRP levels ($p < 0.0001$). Patients with HS exhibited the highest CRP concentrations, significantly exceeding controls ($p < 0.0001$) and IS patients, IS patients showed significant elevation compared to controls ($p < 0.0001$), as shown in Table 2 and Figure 3.

Table 2. Serum levels of Glial Fibrillary Acidic Protein, IL-6 and CRP in the patients and the control groups:

Biomarkers	Control (n=25)	IS patients (n=25)	HS patients (n=25)	P-value
GFAP(pg/ml)	141.7 a (126.4-153.5)	330.5 b (314.8-376.1)	381.8 b (332.1-407.0)	**<0.0001
IL 6 (pg/ml)	17.13 a (14.87-17.93)	31.45 b (30.07-33.46)	40.60 b (30.62-45.02)	**<0.0001
CRP (ng/ml)	3.69 a (3.06-4.22)	7.88 b (7.24-8.43)	10.24 c (9.34-10.70)	**<0.0001

Data were expressed as median(interquartile); p value < 0.05 is considered as statistically significant; Median followed by different letters are significantly different and Median followed by the same letter are not significantly different; GFAP: glial fibrillary acidic protein; IL-6: interleukin 6; CRP: C-reactive protein.

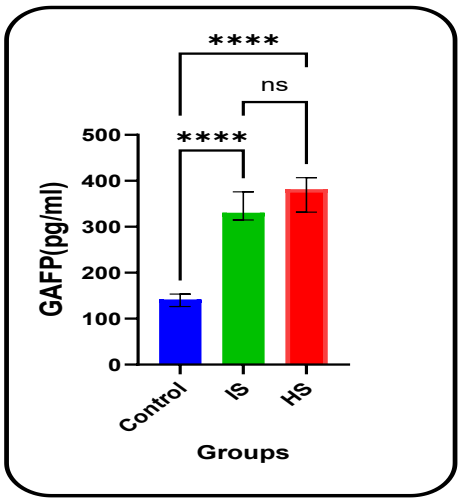

Figure 1: Serum level of GFAP among the patients and the control groups. ns: no significant difference; ** Extremely highly significant (P ≤ 0.0001)**

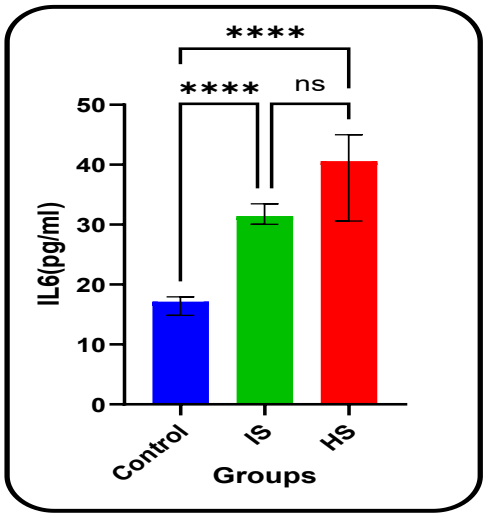

Figure 2: Serum level of IL6 among the patients and the control groups. ns: no significant difference; ** Extremely highly significant (P ≤ 0.0001).**

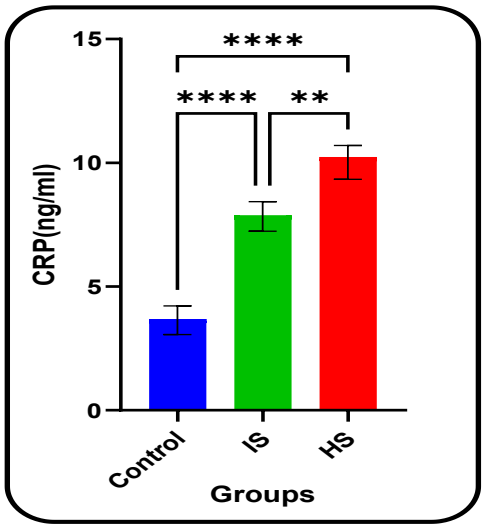

Figure 3: Serum level of CRP among the patients and the control groups. ** Extremely highly significant (P ≤ 0.0001).**

Receiver Operating Characteristic (ROC) of GFAP:

Receiver Operating Characteristic ROC curve analyses of GFAP demonstrated that GFAP levels were able to distinguish patients with IS from controls, with an area under the curve of 1 (95% CI 1.00 to 1.00), with 100% sensitivity and 96% specificity, cut off values were (> 169.3), Figure (4a). Furthermore, GFAP levels were able to discriminate patients with hemorrhagic stroke from controls, with an area under the curve of 1.00 (95% CI 1.00 to 1.00), 100% sensitivity and 100% specificity, Figure (4b). The area under GFAP for discriminating between IS and HS patients were 0.7385 (95% CI 0.5995-0.8774) with ($p < 0.001$). More specifically, using a cut-off point of ≥235.26 pg/ml GFAP was able to acceptably differentiate patients with IS from those with HS with a sensitivity of 84.62% and a specificity of 73.08% Figure (4c).

Table 3. Receiver Operating Characteristic curve data of GFAP:

Biomarker	Group	AUC	Explanation	P-value	Best cut off	Sensitivity	Specificity
GFAP	IS vs control	1	excellent	<0.0001	>169.3	100%	96%
	HS vs control	1	excellent	<0.0001	>149.2	100%	100%
	IS vs HS	0.7385	acceptable	0.0035	≥235.26	84.62%	73.08%

AUC: area under the curve; GFAP: glial fibrillary acidic protein; IS: ischaemic stroke; HS: hemorrhagic stroke.

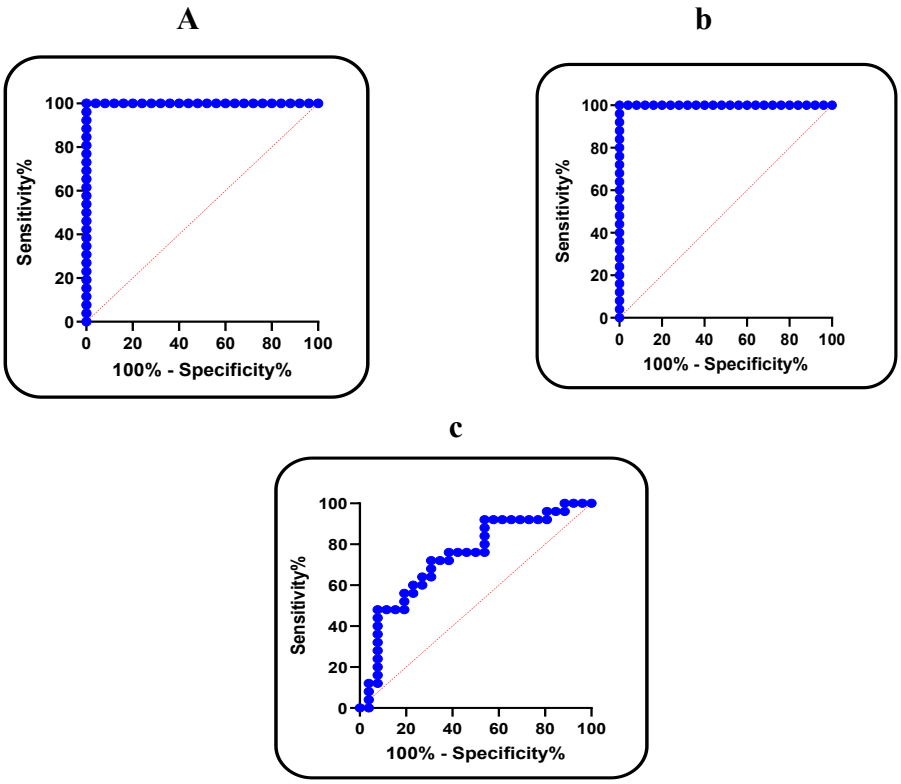

Figure 4: Receiver Operating Characteristic curve of GFAP; a: ROC curve of IS versus control, b: ROC curve of HS versus control; c: ROC curve of IS versus HS.

Correlation between GFAP with IL6 and CRP:

The present study have shown no significant correlation between GFAP and each of IL6 and CRP ($p > 0.05$), as shown in Table 4.

Table 4. Spearman correlation among the studied biomarker:

Variable 1	Variable 2	r Value	P Value	Correlation Type
GFAP (pg/ml)	IL6(pg/ml)	0.007	0.9726	No/Very Weak
GFAP (pg/ml)	CRP (ng/ml)	0.242	0.2441	No/Very Weak

Correlation is significant at the 0.05 level; R: Pearson correlation coefficient; GFAP: glial fibrillary acidic protein; IL-6: interleukin 6; CRP: C-reactive protein.

Association between GFAP Levels and clinical parameters in studied group:In the current study, it was found that there were no significant associations between GFAP and each of hypertension, diabetes, smoking, family history and **previuos stroke** (p value>0.05).

Table 5. Association between GFAP Levels and clinical parameters in stroke patients:

Biomarker	Risk Factor	group	n	Level	T or U test	P
GFAP	**HTN	positive	48	342.6(394.1-320.61)	67.5	0.367
		negative	2	385.2(388.6-381.8)		
	*DM	positive	25	353.18±48.18	-0.608	0.546
		negative	25	361.66±49.78		
	*Smoking	positive	25	347.61±45.84	-1.432	0.159
		negative	25	367.24±50.95		
	*Family history	positive	20	345.67±36.32	-1.399	0.168
		negative	30	365.26±55،05		
	*Previuos stroke	positive	20	355.97±47.55	-0.169	0.866
		negative	30	358.39±50.7		

*The data were expressed as Mean ± SD; **data were expressed as median (iterquartile range);mann whitney U test to compare between groups of not normally distributed data; p value < 0.05 is considered as statistically significant; GFAP: glial fibrillary acidic protein; DM: diabetes mellitus; HTN: hypertension

Discussion:

Early diagnosis of stroke is very important since treatment of ischaemic stroke depend on time and this will improve functional outcome of patients suffering from IS. In the brain there is unit called neurovascular unit which is consist of neurons, asrtocyte, microglia, endothelial cells, pericyte as well as vascular smooth muscle cells(20). Blood brain barrier consist of number of cells one of these are astrocyte end feet, BBB protect the brain from toxins and dangerous chemicals(21). Finding biomarkers specific to stroke is very difficult due to mutiple causes one of these there are multiple stroke types, mainly ischaemic and hemorrhagic, each type has its distinct mechanism and subtypes. Furthermore, there are different types of cells inside the brain including neurons, endothelial cells, astrocyte and other types and each contribute in different way to the pathophysiology of stroke. So biomarkers must provide rapid information about type of stroke, where speed is essential for treatment(20). Distinguishing ischemic from hemorrhagic stroke is important as it guides therapeutic decisions. Patients with ischemic stroke benefit from intravenous thrombolysis, which is contraindicated in hemorrhagic stroke. Currently, a plain CT scan of the head is used to identify hemorrhagic stroke. Studies have explored the use of biomarkers to quickly rule out an intracerebral hemorrhage (ICH). Such biomarkers could be useful in remote regions where transfer to the nearest hospital with CT scanner may require several hours (22). In the current study, we investigate role of GFAP as diagnostic biomarker to differentiate IS from HS. Because cell death and cell lysis may be slowed in case of

ischaemic stroke, this led to difference in release of this glial protein so this could create diagnostic window between hemorrhagic and ischaemic stroke(22). This study was discovered that, there was no statistically significant difference in the concentration of GFAP between ischaemic and HS. In case of stroke disturbance of BBB lead to passage of GFAP into cerebrospinal fluid after that it will pass into blood. After 12 hours of onset of IS symptom GFAP can be found in the blood and reach its maximum concentration after 48 hours of IS onset. Glutamate excitotoxicity that occurs during pathophysiology of stroke cause astrocytes hyperreactivity and which is called astrogliosis. This astrogliosis cause rapid elevation in concentrations of GFAP, moreover damaged astrocytes also release GFAP(14). While in case of HS due to acute brain damage occurred following rupture of blood vessels and the immediate disturbance of the brain blood barrier and astrocyte is part of BBB so there will rapid damage to these cells and GFAP will be rapidly increased(23). There was a study where 187 IS patients and 63 patients ICH were recruited in the study, which found higher GFAP levels, among patients with ICH, although it could not reach a statistical significance (P = 0.09) (24) and result is consistent with this study. However, this study's result is not consistent with result of study done by Bustamante A et al, they detected that patient with ischaemic stroke had lower concentration of GFAP compared to patient with ICH, this may be due to time of sample collection, Bustamante A et al collected the serum within 4.5 hours and in the present study the samples were collected within 24 hours (25). In addition, Katsanos et al, found that median plasma concentration of GFAP in ICH is high when compared to patients with acute ischaemic stroke, stroke mimics, and controls (P<0.001), these researchers were collected samples within 6 hours of symptom(26). Regarding ROC curve the present study found that GFAP could diagnose IS from HS with AUC of 0.7385, p-value =0.0035, cutoff ≥235.26pg/ml, sensitivity of 84.62% specificity of 73.08%, so it had acceptable discrimination ability to differentiate between IS and HS. A study done in Italy by luger S et al, within 6 hour of symptom found that area under cuvre of GFAP for distinguishing IS from HS was 0.872 (95% CI, 0.802–0.942), P<0.001 with cutoff value of 0.03µg/l, sensitivity of 77.8% and a specificity of 94.2%(27). Furthermore, a study found that the optimal GFAP cut-off level to discriminate intracranial hemorrhage from ischaemic stroke and stroke mimics conditions within 12 hours of symptom onset by ROC analysis was 0.57 µg/l and area under the curve(AUC) was 0.871 [95% CI 0.810–0.933], (p<0.001)(28). So there is difference in median, cut off value, sensitivity and specificity between studies and this is may be due to different sample size and differences in sampling time also due to difference in size of hematoma and infarct size. With regarding to inflammatory codition in stroke, this study observed extremely significant elevation of IL6 and CRP in both patients with ischaemic and hemorrhagic stroke and this is as expected because inflammation occur as part of pathophysioloy of stroke. A study found that IL-6 can be detected in the blood sample as soon as 20 minutes of symptom, and the level of some inflammatory factors continue to increase when second blood sample was obtained during the first 24 hours and this is consistent with the current result (29). Other studies focused on the role of IL6 and CRP to predict outcome and severity of stroke, some studies found that there is positive corrrlation between stroke severity and IL6, the level of IL6 was higher in patient with recurrent stroke(30). Another study found that follow-up (in the following day after 24 hour of symptom) CRP is strongly associated with functional outcome, symptomatic ICH, and mortality after 90 days in patients received thrombolytic therapy(31). Other study noted that higher

IL6 associated with poor prognosis(32). In the present study, it was demonstrated that there is no significant correlation between GFAP and each of CRP and IL6. There was no previous study about this. A study found that there was no correlation between CRP and S100B in IS patients which also an astroglial protein(33). Besides, the present study revealed no significant association between GFAP level and daibetic patients and this disagree with a study which found that group in which GFAP concentrations were elevated had higher diabetes mellitus proportion ($P =$ 0.017) (34). Also, the current study detected insignificant association between GFAP level and hypertension, and this is consistent with a study where a binary logistic regression analysis did not show that high blood pressure to independently influence GFAP plasma concentrations(35). Moreover, this study noted no statistically marked association between GFAP levels and each smoking and previous stroke, and this disagree with a study in term of previous stroke which found that in IS patients, the median serum GFAP level was significantly higher in subjects with history of stroke compared to those with a no previous stroke(36). Furthermore, a study done in patients with heart failure in whom cognitive impairment occur, GFAP was found to be affected by smoking(37) however, there were no previous studies reported association between smoking and GFAP in stroke patients.

Conclusion:

In conclusion, GFAP could be used to differentiate stroke from control, and have acceptable discrimination ability to differentiate IS from HS. Further studies are required with larger sample size to validate the result and further studies are required to investigate newer biomarkers with a higher differentiation ability for diagnostic use.

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