



High Specific C-Reactive Protein in Prediction of the Early Outcome of Primary Intra Cerebral Hemorrhage

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Authors' contributions

This work was carried out in collaboration between all authors. Author KE designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Authors MG and YI managed the analyses of the study. Author MS managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: Primary intra cerebral hemorrhage (ICH) has high rate of disability and death. Many factors was supposed to be predictors of the outcome. The significance of measuring C-reactive protein (CRP) levels to predict the outcome is uncertain, and data have been controversial. The objective of our clinical study was to determine the relationship of hs-CRP levels with bad outcome. The authors tested if (independent of confounding factors) hs-CRP levels was elevated on admission (< 24 hours after ictus). Fifty patients with acute spontaneous hemorrhagic stroke, within 24 hours of onset confirmed by CT brain were admitted at neurology department, Mansoura University Hospital from June 2017 to September 2018. Age and sex cross-matched 50 healthy persons were studied as control group. Patient and control groups were subjected to full history, general and neurological examination, GCS on admission, National Institute of Health Stroke Scale (NIHSS) on admission, ICH score and Canadian scale on admission and after 30 days, Venous Blood samples were taken within 24 hours of onset and tested for routine laboratory investigations

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(liver function, serum creatinine, CBC and blood glucose) and High Sensitive C-Reactive Protein level using Enzyme Immunoassay Test Kit. Computed tomography (CT) brain was repeated 72 hours later. Multivariable regression analyses were used to evaluate associations of hs-CRP concentration and ICH outcome. Kaplan–Meier analysis was used for survival.

Results: This study revealed that Hs-CRP is significantly higher in patient group (9.3 mg/l) when compared to control group (0.68 mg/dl) with p value < 0,001. There was statistically significant correlation between NIHSS and hs-CRP levels but there was no statistically significant correlation between hs-CRP levels and stroke outcome.

Conclusion: Taking these covariates into multivariable analysis revealed that there is correlation between hs-CRP and hemorrhagic stroke but it cannot be used as a predictor of its outcome.

Keywords: Cerebral hemorrhage; neurological disorder; mortality; hypertension; acute stroke.

ABBREVIATIONS

ICH : Primary intra cerebral hemorrhage.
CRP : C-reactive protein.
hs-CRP: high specific C-reactive protein.
GCS : Galascow coma score.
NIHSS : National Institute of Health Stroke Scale.
CT : Computed tomography.
CNS : central nervous system.
ICH : intra cerebral hemorrhage.
SAH : subarachnoid hemorrhage.
ESR : erythrocyte sedimentation rate.
WBC : white blood cell.
IL-6 : interleukin-6.
EHG : Early Hematoma Growth.
ENW : early neurological worsening.
ELISA : enzyme linked immunosorbent assay.
ROC : Receiver Operating Characteristic.
BMI : body mass index.
AUC : Area under curve.
VKA : vitamin K Antagonist.

1. INTRODUCTION

Stroke is a life threatening neurological disorder. It is one of the important reasons of morbidity and mortality worldwide [1]. Stroke is classically characterized by a neurological deficit attributed to an acute focal injury of the central nervous system (CNS) due to a vascular cause, including cerebral infarction, intra cerebral hemorrhage (ICH), and subarachnoid hemorrhage (SAH) [2].

Stroke can be classified into two main classes: ischemic and hemorrhagic. Common causes of primary ICH include hypertension, amyloid angiopathy, coagulopathy, vascular anomalies and tumors. 70-90% of cases of primary ICH caused by arterial hypertension, while spontaneous ICH comes in second place [3].

The importance of laboratory parameters as a predictor biomarkers in acute stroke was not accessed sufficiently [3]. The first hours after an acute stroke are critical, as it is the effective intervention time. Several studies had discussed the predictive value of numerous laboratory parameters as erythrocyte sedimentation rate (ESR), total leukocyte count, and blood glucose level [4].

C-reactive protein (CRP) is a glycoprotein produced by the liver, which is normally absent from the blood. It is an acute-phase serum protein and a member of the pentraxin protein family [5]. CRP, named for its ability to somatic C-polysaccharide of *Streptococcus pneumoniae* precipitation, was the first acute-phase protein and is a sensitive systemic inflammatory and tissue damage marker [6].

CRP typically increases within six hours from the inflammation onset. There are 2 CRP types, the standard CRP is used to determine the inflammation activity as in chronic disorders as arthritis; to detects the new infection; and to monitor the treatment response of these disorders. The other CRP type is high-specific CRP (hs-CRP), which considered as a low-grade vascular inflammation marker, which is a principle factor in the atherosomatous plaques development and rupture [5].

Inflammation is a major characteristic factor of the pathology of primary ICH & inflammatory markers on admission as raised white blood cell (WBC) count, fibrinogen and interleukin-6 (IL-6), and are related to bad short-term outcomes. CRP is related to thirty-day mortality in ICH cases, but its relationship with Early Hematoma Growth (EHG) is not reported [7]. Although some studies used increased level of CRP for determining the outcome of ischemic stroke, no comparative study on serum level of

hs-CRP level as an indicator for differentiation of ischemic from hemorrhagic stroke were found [5].

1.1 Aim of the Work

Our aim is to detect the relationship between high specific CRP (Hs_CRP) and early hematoma growth (EHG), early neurological worsening (ENW) and use it to predict the early outcome of primary intra cerebral hemorrhage.

2. METHODS

2.1 Patient Population

Our prospective clinical study was conducted on 50 patients with spontaneous ICH admitted at neurology department, Mansoura University Hospital from June 2017 to September 2018, and 50 healthy persons were examined at neurology department (control group). The exclusion criteria were ischemic stroke, history of acute or chronic infections (≤ 4 weeks before spontaneous ICH), patient with other concurrent comorbidities capable of increasing inflammation markers, Patient with obvious signs and clinical evidence of acquired in-hospital infection, a delay after passage of the first 24 hours after onset of stroke, patients with secondary causes of intra cranial hemorrhage as receiving anticoagulants before admission, patients having conditions known to affect coagulation, such as sepsis, malignancy, acute venous thromboembolism, hypercoagulable state, collagen diseases, recent surgery or trauma within 30 days and myocardial infarction within 10 days, severe coma or terminal illness and patient refusal to participate in the study.

The study was approved by the Institutional Review Board of Faculty of Medicine, Mansoura University, Egypt.

2.2 Clinical Data

The patient's clinical state was recorded on admission including full history, general and neurological examination, GCS on admission, NIHSS on admission, ICH score and Canadian scale on admission and 30 days, venous Blood samples were taken within 24 hours of onset for routine laboratory investigations (liver enzyme, serum creatinine, CBC and blood glucose, hs_CRP which was analyzed using enzyme linked immunosorbent assay (ELISA).

Computed tomography (CT) brain will be done on admission and 72 hours later. Patients in the two groups will be compared for severity, neurological functions worsening and mortality rate after 30 days.

Past history of hypertension or Diabetes mellitus, and anticoagulants and other medications use was evaluated.

2.3 Statistical Analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 22.0. Qualitative data were described using number and percent. Quantitative data were described using median (minimum and maximum) & inter quartile range for non-parametric data and mean, standard deviation for parametric data after testing normality using Kolmogrov-Smirnov test. Significance of the obtained results was judged at the (0.05) level and using Receiver Operating Characteristic (ROC) curve analysis and Linear regression analysis to detect the diagnostic accuracy.

3. RESULTS

In our studied patients the age range was 50-78years (mean \pm SD = 65.32 \pm 4.23years), 55% were male and the mean BMI was 27.54 \pm 5.99 (range19-37.4). There were no statistically significant differences found between the studied groups (p value $>$ 0.05).

Hs-CRP is significantly higher in patient group (9.3 mg/l) when compared to control group (0.68 mg/dl) with p value $<$ 0,001. Table 1.

AUC (Area under curve) and characteristic performance of hs-CRP for discrimination between patient and control group show that good AUC is found (AUC=0.998, p $<$ 0.001). At cut off value of 1.846, sensitivity is 98.0%, specificity is 92.0%, PPV is 97.9%, NPV is 92.5% and accuracy is 95.0%. Table 2.

There were no significant differences were found in age according to hs-CRP in all studied cases, but there was statistically significant difference with clinical presentation mainly in acute left sided hemiparesis and acute right sided hemiparesis, and there was no significant difference were found in patients with chronic liver disease, Smoker, DM, HTN. Table 3.

Hs-CRP has significant difference with NIHSS, with no significant factor with GCS, Canadian scale at onset and 30 days after. Table 4.

Hs-CRP has no statistically significant correlation with mortality rate among studied cases. Table 5.

After multivariate regression analysis we noticed that there is correlation between hs-CRP and hemorrhagic stroke but not used as a predictor to outcome of it. Table 6.

4. DISCUSSION

Primary intra cerebral hemorrhage (ICH) has high rate of morbidity and mortality. The cerebral damage that develop after intracerebral hemorrhage is supposed to occur secondary to ischemic, cytotoxic, and inflammatory changes in the underlying and surrounding brain tissue. Recently, there have been many researches that discussed the different inflammatory biomarkers that emerge during cerebral stroke.

Table 1. Comparison of Hs-CRP between cases and control groups

	Control	Cases	Test of significance
Hs_CRP Median (Min-Max)	0.68(0.12-2.15)	9.3(1.82-15.52)	z=8.6 p<0.001*

*Data are compared using Man Whitney U test *statistically significant (p<0.05)*

Table 2. Validity of Hs-CRP in differentiating cases and control groups

	AUC P=	Cut off point	Sensitivity	Specificity	PPV	NPV	Accuracy
Hs CRP	0.998 <0.001*	1.846	98.0%	92.0%%	97.9%	92.5%	95.0%

AUC: Area Under Curve; PPV: Positive predictive value; NPV: Negative predictive value

Table 3. Relation between hs-CRP & age, clinical presentation and risk factors

	Hs CRP	Test of significance	P
Age /years <60 ≥60	9.3(3.96-15.52) 9.3(1.82-15.5)	Z=0.31	P=0.75
clinical presentation ALH ARH Recurrent stroke Acute onset dysarthria Symptomatic epilepsy	11.73(3.96-15.5) ^A 8.32(1.82-15.5) ^A 15.52(15.52-15.52) 6.45(4.5-8.4) 15.5(15.5-15.5)	KW	P=0.028*
Risk factors CLD -VE +VE	9.3(1.82-15.5) 8.46(4.5-12.41)	Z=0.63	P=0.53
CKD -VE +VE	9.3(3.4-15.5) 15.5(1.82-15.5)	Z=1.00	P=0.32
SMOKER -VE +VE	9.3(1.82-15.5) 9.12(4.1-15.5)	Z=0.38	P=0.71
DM -VE +VE	9.3(1.82-15.5) 9.3(4.1-15.5)	Z=1.11	P=0.27
HTN -VE +VE	8.87(3.96-15.5) 9.3(1.82-15.5)	Z=0.16	P=0.87

Data are compared using Mann Whitney test (z) and Kruskal Wallis test (KW);ALH: acute left hemiparesis; ARH: acute right hemiparesis; CLD: chronic liver disease; CKD: chronic kidney disease

Table 4. correlation between hs-CRP &GCS, NIHSS, Canadian scale

Hs CRP		
	r	p
GCS	-0.09	0.54
NIHSS	0.397	0.004*
Canadian scale at onset	0.13	0.36
Canadian scale 30 days after	0.05	0.74

Data are compared using Spearman correlation coefficient

Table 5. Hs -CRP association with mortality among studied cases

	Alive n=46	Dead n=5	Test of significance
Hs -CRP Mean ± SD	10.12 ± 4.21	9.62±5.54	t=0.25 p=0.81

t: Student t test

Table 6. linear regression n in prediction of NIHSS

a. Dependent variable: NIH						
Model	Unstandardized coefficients		Standardized coefficients	t	P	
	B	Std. Error	Beta			
1	(Constant)	11.275	.962		11.716	.000
	HS_CRP	-.026	.034	-.108	-.751	.456

F=0.56 P=0.46
R2=0.108

As regards ischemic stroke, bad outcome and higher incidence of recurrence was linked to the pro-inflammatory cytokine C-reactive protein (CRP), [8,9]. The higher the CRP levels in acute ischemic stroke patients the larger the infarct volume, and CRP levels > 1.5 mg/dl at discharge was associated with occurrence of other vascular events later on as transient ischemic attacks, cerebral stroke, myocardial infarction or Angina) and/or death after one year [10].

As regards ICH, the value of C-reactive protein (CRP) levels in predicting outcome is unclear, and findings have been contradictory. CRP was linked to 30-day mortality and added 8% improvements in the accuracy of the ICH score [11] and also it was noticed that CRP > 5 mg/dL on admission and at 72 hours later was linked with worse Glasgow Outcome Score and also worse survival after six months [12].

The objective of our clinical study was to determine the relationship of hs-CRP levels with bad outcome.

Hs-CRP levels were significantly elevated in patients with hemorrhagic stroke when compared with the healthy controls, these data were contradictory to Roudbary and his colleagues study that revealed that hs-CRP level increase in

patients with ischemic infarction dramatically but not in hemorrhagic stroke which might be considered as a usefully adjunct method for determining type of stroke in patients with cerebrovascular problems not as a predictor for neurological outcome. This study was done on patients with ischemic and hemorrhagic stroke at neurology department of Poursina Hospital, Iran but they worked on small sample of patients (The total studied sample consisted of 32 patient). In addition, they did not follow neurological deterioration of their cases. [5]

LöPPönen and his colleagues found that there was significant difference with diabetes mellitus, warfarin medication but this study was done for assessment of predictive value of conventional CRP for the outcome after primary intra cerebral hemorrhage not hs-CRP.[3]

In our study, we found that hs-CRP level was significantly high with some clinical presentations with p value=0.028, we found that recurrent stroke and acute symptomatic epilepsy were associated with higher level of hs-CRP (15.5 mg/dl) followed by acute left side hemiparesis presentation (11.73 mg/dl), acute right sided hemiparesis (8.32 mg/dl) then acute onset dysarthria (6.45 mg/dl).

Our study revealed no statistically significant correlation between serum hs-CRP level measured within 24 hours of stroke onset and the GCS on admission. This was contradictory to Löppönen who made their study on 961 patients, their results showed that the higher CRP value on admission, the lower GCS score with $p < 0.001$ but they had worked on conventional CRP.[3]

Our study revealed that there is statistically significant correlation between serum hs-CRP level measured within 24 hours of stroke onset and NIHSS results on admission, Higher Hs-CRP levels with higher NIHSS score with p value 0.004.

We found no statistically significant correlation between serum hs-CRP level measured within 24 hour of stroke, ICH score results on admission and after 30 days and the Canadian scale results on admission and after 30 days. These data were contradictory to Di Napoli and his colleagues studies that revealed that Plasma CRP increased over the 48 hours from admission and there was statistically significant correlation between plasma hs-CRP level over 48 hours and the size of hematoma ($p < 0.001$) and Di Napoli and his colleagues who reported that the presence of CRP could be due to local synthesis stimulated by the hematoma itself or the circulating soluble pentameric form transformation into monomeric and insoluble form. Also, reported the role of CRP in expansion of the damage.[13,14]

Di Napoli noticed that adding hs-CRP level plus the ICH-score considerably elevated the ability to predict 30-days death rate by 8%. It was reported that the prognostic accuracy was greater in cases with low to moderate risk by the ICH-score alone compared with the highest risk cases, in whom the severity of ICH could be the main death indicator, and the lowest risk group, in which other diseases could represent the main prognosis indicators.[14]

Our study revealed on statistically significant correlation between serum Hs-CRP levels measured within 24 hours of stroke and CT brain finding or hematoma growth rate. These data were contradictory to Rajapathy study which is a prospective study at Sarawak General Hospital, Malaysia. Sixty cases with supratentorial hematoma within 1 day after the onset were recruited to detected morbidity and mortality at six months.[15]

Regression analysis, which was, conducted for prediction of intracranial hemorrhage outcome in relation to NIHSS within studied cases, revealed no statistically significant correlation between them and serum hs-CRP level. So, high plasma hs-CRP level on admission is an independent predictor of an unfavorable result and is only slightly associated with the clinical and radiological severity of the bleeding.

This is in agreement with study done by Löppönen and his colleagues study that showed that regarding to age, sex, GCS score, vitamin K Antagonist (VKA) use, hematoma size, intra-ventricular hemorrhage, midline shift, sampling time and WBC, CRP > 10 mg/L independently predicted the growth of the hemorrhage and neurological deterioration both of which raised the mortality risk but in these study CRP was detected by a turbidimetric method.[3]

This is in agreement with study done by Elhechmi study that was performed on 223 patients. CRP was measured at admission, 24, 48, and 72 hours after the onset of ICH. It raised significantly from 48 to 72 hours from admission, and the intensity of the response was associated with size of the hematoma but also, in this study CRP was measured by turbidimetric method.[16]

Our study revealed that higher CRP concentrations were related to higher mortality rate and bad outcome at 1 month. From a clinical vision, it is important to declare that measurement of serial hs-CRP during ICH course could provide more accurate predictive utility: hs-CRP values on admission were only weakly associated with mortality and did not predict functional status, CRP at 24 hours was a better predictor of poor outcome and the mortality rate and predictability improved further with the CRP levels results at 48 or 72 hours that was stronger for mortality rate than for functional recovery But These data were contradictory to Alexandrova study who worked on 46 ICH cases within 48 hours after onset and shown that serum CRP level on admission is a strong predictor of short-term fatal outcome.[17]

Lifestyle and food habits can influence CRP. The high CRP level further promotes the concept of existence of cerebral inflammatory process after hemorrhagic stroke [18,19]. Recording this elevated level gives rise to the hope of CRP-lowering drugs for protecting high-risk individuals. Many factors can help lowering CRP levels like exercise, weight loss, diet [20] and some drugs as angiotensin-converting

enzyme inhibitors/angiotensin receptor blockers, antihyperlipidemics, antidiabetes, antiinflammatory (cyclooxygenase inhibitors), and antiplatelet agents (clopidogrel, abciximab) [21]. Vitamin C may be another successful drug through reducing CRP levels [22,23] but further studies focusing on all these factors influencing CRP levels and their prophylactic role on hemorrhagic stroke are needed.

5. CONCLUSION

Taking these covariates into multivariable analysis revealed that there is correlation between hs-CRP and hemorrhagic stroke but it cannot be used as a predictor for its outcome.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

An informed consent was taken from all patients or their family.

ETHICAL APPROVAL

The protocol was approved from Faculty of Medicine Ethics Committee for Human Research to determine the possibility of using hs CRP as a predictor for the outcome after primary intracerebral hemorrhage.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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