Zagazig University Medical Journal
www.zumj.journals.ekb.eg
https://doi.org/10.21608/zumj.2024.234154.2873 Volume 30, Issue 7, Oct. 2024
Manuscript ID ZUMJ-2407-3473 DOI . 10.21608/ZUMJ.2024.303983.3473
ORIGINAL ARTICLE

Serum Biomarkers Predicting Prognosis of Spontaneous Intracerebral Hemorrhage

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Submit date: 13-07-2024
Revise Date : 19-07-2024
Accept date: 21-07-2024

ABSTRACT

Background: Intracranial hemorrhage (ICH) carries a high risk for mortality and morbidity. Identification of reliable predictors of outcome are important to optimize treatment. **Aim**: The Aim of our study was to identify the impact of platelet count and volume; neutrophil /platelet ratio (NPR) and LDL cholesterol (LDL-C) at admission on the short term clinical outcome of ICH. **Methods:** A total of 138 adult patients with definite diagnosis of ICH were recruited to this study. The clinical characteristics and the previously mentioned laboratory markers were assessed and correlated with the short term outcome determined by the modified Rankin Scale (mRS) after one month of onset. **Results:** No significance was observed between platelet count and volume; NPR, and poor prognosis of stroke. Hypertension, high National Institute of Health Stroke Scale (NIHSS) score on admission were significantly related to bad prognosis (P = 0.045, 0.01 respectively); in addition to higher levels of INR and lower levels of LDL-C (P = 0.02 and .002 respectively). **Conclusion:** Poor outcome after ICH was related to severity at onset assessed by NIHSS. Hypertension, bleeding tendency and lower LDL-C levels were also independent factors for poor outcome.

Keywords: Stroke; NPR; Outcome, Predictors.

INTRODUCTION

Intracerebral hemorrhage (ICH) is a serious public health concern which showed a steady increase in numbers over the last few decades **[1].**Although ischemic stroke has a greater incidence rate, ICH has a higher risk of mortality and morbidity, placing an increasing strain on healthcare systems and economies **[2].**

An elevated risk of ICH had been linked to impaired platelet function **[3].**In addition, studies showed that the underlying cause of persistent bleeding in ICH patients is connected to systemic inflammatory responses **[4]** and one indicator of this systemic inflammation is the neutrophil /platelet ratio (NPR). The interaction between neutrophils and platelets mediates the vascular damage following cerebral infarction **[5].**Furthermore, elevated NPR was an

independent indicator of hemorrhagic transformation following ischemic stroke **[6].** Serum lipid levels have been demonstrated to be linked to the development of ischemic stroke and cardiovascular disease **[7].**However, it is still unknown how serum lipid concentrations and ICH are related. A number of researches have indicated that low blood cholesterol and statin medication may be linked to an elevated risk of ICH and unfavorable outcomes **[8].** Some have challenged these results and suggested that people with ICH might benefit from reduced serum cholesterol and statin use **[9].**

METHODS

We prospectively included 138 patients with ICH who were admitted to intensive care units of Zagazig University Hospitals.The study protocol (ZU-IRB#11370) was approved by the ethical committee.

Informed consent was taken from the relatives mainly or from patients if available. Inclusion criteria were: Age more than 18 years, patients with ICH diagnosed by performing computed tomography (CT) of the head within 24 hour of admission. We excluded subjects with traumatic brain hemorrhage, ICH related to aneurysm or arteriovenous malformation, brain tumors, systemic diseases like cancer, hematological malignancies, autoimmune diseases and recent infectious illness. Upon admission to the hospital, baseline clinical and demographic parameters were collected including age; sex; body mass index (BMI); blood pressure; alcohol and cigarette use; and the medical history of comorbidities such as previous ischemic stroke or transient ischemic attacks; hypertension; diabetes mellitus, cardiac problems and dyslipidemia. The patients' state of consciousness was assessed using the Glasgow Coma Scale (GCS) **[10].**The National Institutes of Health Stroke Scale (NIHSS), comprising fifteen questions with a severity range of 0 to 42, was used to assess the severity of strokes. A mild stroke or no symptoms is represented by a score of less than 5, a moderate stroke is represented by a score of 5 to 15, a moderate to severe stroke is represented by a score of 16 to 20, and a severe stroke is represented by a score of 21 to 42 **[11].**The degree of disability was evaluated using the modified Rankin Scale (mRs). There are six scores available, ranging from 0 to 5. A score of 0 indicates no symptoms, while a score of 5 indicates severe disability. Death received a score of 6 **[12].**Within the 24 hours of admission, a blood sample was withdrawn for the following: Complete blood picture including platelet count and volume, hemoglobin, neutrophil, lymphocyte and monocyte counts, blood glucose level and lipid profile. Prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR) were done. The ratio of the Absolute neutrophilic count (ANC) × 100 to the platelet count was used to calculate the admission NPR **[13].** Meanwhile, radiological data was recorded using an axial brain CT scan without contrast. Hemorrhage site; whether supratentorial or infratentorial was determined and ischemic stroke was excluded. The ABC/2 formula was used to calculate the volume of the hematoma: A = longest diameter, B = diameter perpendicular to A, and C = number of slices multiplied by thickness **[14]** andbased on it, subjects were grouped as small (<20 cc), moderate (21-40 cc) and large (>40 cc) **[15].**

Functional outcome was evaluated after 3 months of onset based on the results of the mRS and was correlated with clinical and laboratory markers.A score more than 2 was defined as poor outcome**[16].**

STATISCAL ANALYSIS

Statistical Analysis were performed for the clinical and demographic data of patients. They were presented using median (IQR) or number (%). Differences between the groups were compared using the Wilcoxon Rank Sum Test, Chi square and Fisher exact test. Univariate and multivariate regression analysis were performed with significance at P less than 0.05 and confidence intervals at 95%.

RESULTS

Based on the inclusion criteria, a total number of 138 hemorrhagic stroke patients (47 males and 91 females) were enrolled in the study. **Table (1)** showed the demographic and clinical data of the study subjects. The median age, BMI of our patients were 62 years (IQR, 56-66), 30 (IQR 29-30) respectively. History of comorbidities were assessed in all subjects. Hypertension was detected in 94 (68.1%). Diabetes was present in 91 (65.9%) and dyslipidemia in 39 (28.3%) of cases. Median NIHSS at admission was 16 (IQR 12-24).

Table (2) showed that Supratentorial hemorrhage represented the majority of cases, 128 (92.8%). ICH volume was determined in all cases and included 29 cases (21%) with small volume, 71 cases (51.4%) with moderate volume and 38 cases (27.5%) with large volume hemorrhages. **Table (3)** described the whole measured laboratory parameters in our study and included platelet count, platelet volume, absolute neutrophilic count, absolute lymphocytic count, absolute monocytic count, neutrophil /platelet ratio (NPR). In addition, complete lipid profile including median cholesterol, triglyceride, LDL-C, HDL-C levels were determined (200,121.5,111, 46.4 respectively).

Platelet count; platelet volume; NPR and LDL-C levels were the main studied laboratory parameters. There was no significant association between the previously mentioned parameters and gender, history of comorbid diseases like hypertension, diabetes, dyslipidemia, or ischemic heart disease. No significant relationship could be determined between median NIHSS on admission, or volume of hematoma with these laboratory parameters. There was statistically significant association between NPR and smoking (P = 0.023),**Table (4).**

After 30 days of onset, the clinical outcome was assessed using the modified Rankin Scale (mRS) scale. There were 112 cases with a poor prognosis and 26 with a good prognosis. Between the participants with poor and favorable prognoses, there were no statistically significant differences in terms of gender, BMI, smoking, hyperlipidemia, prior history of diabetes, or ischemic heart disease (P > 0.05). History of hypertension, higher NIHSS score on admission were significantly related to poor prognosis (P = 0.045, 0.01 respectively). No relation was observed between PLT count, platelet volume, NPR, and poor outcome after ICH. The hemorrhagic stroke patients with higher levels of INR and lower levels of LDL-C were found to have a significantly poorer outcome (P = 0.02 and .002 respectively) as shown in **Table (5).**

Therefore, history of hypertension, NIHSS score, INR and LDL-C, as a confounding

variables, were included in the univariate and multivariate logistic regression model, **Table (6)**, to assess independent predictors of poor prognosis.

Univariate analysis showed significant association between poor prognosis and higher NIHSS (P = 0.014), lower LDL-C levels (P = 0.038). The multivariate analysis determined that the hypertension, high NIHSS and INR, lower LDL-C levels were significantly related to poor outcome (P = 0.007, 0.010, 0.018, 0.032 respectively).

Table (1): Demographic and clinical characteristics of the studied patients.

Variable	Median (IQR), n (%)
Age, median (IQR)	62 (56-66)
Sex, female, n (%)	91 (65.9%)
BMI, median (IQR)	30 (29-30)
Hypertension, n (%)	94 (68.1)
Diabetes, n (%)	91 (65.9)
Dyslipidemia, n (%)	39 (28.3)
Atrial fibrillation, n (%)	14 (10.1)
Rheumatic heart disease, n (%)	4 (2.9)
IHD, n (%)	25 (18.1)
Cardiomyopathy, n (%)	11 (8)
Previous stroke or TIA, n (%)	16 (11.6)
Smoking, n (%)	49 (35.5)
Alcohol, n (%)	7 (5.1)
NIHSS admission, median (IQR)	16 (12-24)
GCS admission, median (IQR)	9 (8-12.75)
mRS, admission, median (IQR)	4 (3-5)
Systolic blood pressure, median (IQR)	150 (130-170)
Diastolic blood pressure, median (IQR)	90 (90-100)

BMI, body mass index; IHD, ischemic heart disease; TIA, transient ischemic attack; NIHSS, National Institute of Health Stroke Scale; GCS, Glasgow Coma Scale; mRS, modified Rankin scale; IQR interquartile range

Table (2): Radiological data of the studied patients

Variables	Median (IQR), n (%)
Site of hematoma	
Supratentorial	128 (92.8)
Infratentorial	10 (7.2)
Volume of hematoma	
Small	29 (21)
Moderate	71 (51.4)
Large	38 (27.5)

IQR, interquartile range

Table (3): Laboratory data of the studied patients

Variable	Median (IQR)
Platelet count	190 (167-200)
Platelet volume	9.7 (9.03-10.28)
Absolute neutrophilic count	9.5 (8.4-10.2)
Absolute lymphocytic count	1.2 (0.98-1.35)
Absolute monocytic count	0.64 (0.50-0.78)
NPR	7.13 (5.33-8.4)
Random blood sugar	4.44 (3.54-4.91)
Cholesterol	200 (200-234)
Triglycerides	121.5 (110-138.5)
LDL-C	111 (100-129.75)
HDL-C	46.5 (42-50)
PT	14 (12-16)
PTT	103 (101-110)
INR	1.1 (1-1.3)

NPR, neutrophil platelet ratio; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; PT, prothrombin time; PTT, partial thromboplastin time; INR, international normalized ratio.

Table (4): Relationship between platelet count, platelet volume, NPR, LDL-C levels and disease characteristics.

Variables	Platelet count[1]	P value[2]	Platelet volume[1]	P value[2]	NPR[1]	P value[2]	LDL-C[1]	P value[2]
Female sex	187	0.14	9.7	0.08	7.3	.2	111	0.4
Hypertension	190	0.5	9.7	0.8	7.2	.9	114	0.08
Diabetes	190	0.7	9.7	0.8	7.25	0.6	111	0.6
Dyslipidemia	190	0.7	9.7	0.7	7.15	0.8	111	0.5
Smoking	198	0.8	9.7	0.5	6.7	**0.023***	111	0.2
IHD	200	0.12	9.6	0.6	7.8	0.8	100	0.2
NIHSS admission								
Moderate NIHSS	183	0.3	9.65	0.9	7.12	0.6	111	0.3
Moderate to severe NIHSS	190		9.65		7.14		122.5	
Severe NIHSS	198		9.75		7.22		111	
Volume of hematoma								
Small	190	0.2	9.6	0.4	8.01	0.11	111	0.2
Moderate	178		9.7		7.15		115	
Large	198		9.85		6.74		105	

1, median; 2, Wilcoxon rank sum test; IHD, ischemic heart disease; NIHSS, National Institute of Health Stroke Scale; NPR, neutrophil platelet ratio; LDL-C, low density lipoprotein cholesterol.

Table (5): Comparison of clinical characteristics between patients with good and poor outcome.

Variables	Good outcome, N = 26[1]	Poor outcome, N = 112[1]	P value[2]
Female	16 (17.6%)	75 (82.4%)	0.6
BMI	30 (29, 30)	30 (28.75, 30)	0.8
Hypertension	22 (23.4%)	72 (76.6%)	**0.045***
Diabetes	19 (20.9%)	72 (79.1%)	0.4
Dyslipidemia	7 (17.9%)	32 (82.1%)	0.9
IHD	4 (16%)	21 (84%)	0.8
Smoking	8 (16.3%)	41 (83.7%)	0.6
GCS (at admission)	10 (9.25,13)	9 (8,12)	0.062
NIHSS (at admission)	13 (10,15)	18 (12,24)	**0.01***
mRS (at admission)	4 (3,4)	4 (3,5)	0.13
Volume of lesion			
Small	4 (13.8%)	25 (86.2%)	0.5
Moderate	16 (22.5%)	55 (77.5%)	
Large	6 (15.8%)	32 (84.2%)	
Platelet count	177 (158, 200)	190 (167, 200)	0.5
Platelet volume	9.7 (9.14, 10.25)	9.70 (8.90, 10.22)	0.8
NPR	7.25 (5.07, 8.55)	7.00 (5.33, 8.37)	0.6
Cholesterol	200 (184.25, 235)	200 (200, 234)	0.9
LDL-C	120.5 (100, 132.25)	100 (92.50, 110.75)	**0.002***
INR	1 (1, 1.23)	1.1 (1, 1.3)	**0.022***

BMI, body mass index; NIHSS, National Institute of Health Stroke Scale; GCS, Glasgow Coma Scale; mRS, modified Rankin scale, LDL-C, low density lipoprotein cholesterol; INR, international normalized ratio; 1 n (%), median (IQR); 2 Pearson's Chi-squared test; Wilcoxon rank sum test; Fisher's exact test

Table (6): Univariable and multivariable logistic regression of the factors associated with poor outcome according to the mRS at follow up of the studied patients

Variables	OR[1] (univariable)	OR[1] (multivariable)
Hypertension	0.33 (0.09-0.93)[2], P = 0.053	0.18 (0.05-0.58)[2], P = 0.007
NIHSS (at admission)	1.09 (1.02-1.17)[2], P = 0.014	1.10 (1.03-1.19)[2], P = 0.010
LDL-C	1.02 (1.00-1.04)[2], P = 0.038	1.02 (1.01-1.05)[2], P = 0.018
INR	7.97 (1.03-87.94)[2], P = 0.065	13.00 (1.47-173.06)[2], P = 0.032

1Odds Ratio; 295% Confidence interval; NIHSS, National Institute of Health Stroke Scale; LDL-C, low density lipoprotein cholesterol; INR, international normalized ratio

DISCUSSION

Incidence of spontaneous intracerebral cerebral hemorrhage (ICH) was 24.6 per 100,000 people, with high rates of death and disability **[2].**Researchers are still looking for

simple laboratory biomarkers to predict outcomes and guide ICH management **[17,18].**

Platelet count represents a measure of the generation and aging of platelets **[19].** While thrombocytopenia happens concurrently with cerebral hemorrhage **[20],** platelets play a significant role in the etiology of ischemic stroke by forming intravascular thrombus **[21].** The term "mean platelet volume" (MPV) refers to the average size or volume of platelets and is used as a marker for megakaryocytic hyperplasia, metabolism, bone marrow platelet production, and age of circulating platelets **[22].**

Despite being used as indicators of platelet functioning, the association between platelet count; MPV and ICH is still controversial **[23].** Our findings showed that platelet count and MPV had no association with the severity of hemorrhagic stroke as determined by NIHSS (P = 0.3 and 0.9 for platelet count and volume respectively) or the volume of the hemorrhage (P = 0.2 and 0.4 for both respectively). Also they were not related to short term prognosis (P = 0.5 and 0.8 for both respectively).

In contrast to our findings, **DU and colleagues** illustrated that lower MPV may reduce the risk of hemorrhagic stroke, however higher MPV may raise that risk**[23].**Platelet dysfunction was identified in ICH patients, and both low platelet counts and platelet dysfunction might be involved in the expansion of ICH volume **[3].** The differences between studies may be related to variations in methodologies and sample sizes.

In our work there was no correlation between NPR and the prognosis after ICH (P = 0.6). In contrast, a study showed that NPR was independently associated with parenchymal hemorrhage after ischemic stroke (OR = 2.641, P = 0.007) **[6].** Following a stroke, neutrophil activation may play a role in hemorrhagic transformation, weakened blood brain barrier (BBB), and high infarct volume **[24]** as they contributed to the release of inflammatory mediators which augment vessel permeability **[5].** Another study found a significant relation between the admission levels of NPR and hematoma expansion in individuals with ICH **[13].** A greater neutrophil count was related to larger initial ICH volume **[25].** One study reported that the reverse that low neutrophil count was related to an increased risk of growth of hematoma during the hyper acute phase of ICH **[26].** This contradictory results could be explained by the possibility that neutrophil-platelet interaction has distinct vascular inflammation and damage depending on the stage of ICH **[27].**

Our study showed that NPR was significantly related to smoking (P = 0.023). These matched observations from many studies **[28, 29].** Smoking is known to increase systemic inflammation which is mediated by neutrophils and platelets **[30].**

Lipids have been suggested to act as biological markers of ICH severity and our finding determined that lower LDL-C levels were related to poor outcome (P =0.002). Many previous studies suggested that reduced LDL-C levels independently predict hematoma growth, early neurological decline, and poor outcomes after ICH**[31-33]**.It is yet unknown how LDL-C and ICH are related pathophysiological.Because cholesterol is necessary for optimal membrane fluidity, some theories contend that low cholesterol may weaken the endothelium, delay healing and enhance vascular fragility which makes the brain more susceptible to microbleeds **[34].** Furthermore, in a study done by

Mustanoja et al. and after adjusting for known ICH prognostic factors lower LDL-C levels were independently associated with in-hospital mortality of ICH patients **[35].**

Hypertension could predict poor outcome in our work (P = 0.04). In a recent Chinese large sample stroke center study including thousands of ICH patients focusing on the combined effect of both blood pressure and LDL-C levels. The logistic regression analysis determined that ICH patients, who had SBP more than 140 mmHg and LDL-C levels less than 70 mg/Dl, were more likely to experience hematoma growth and in-hospital death **[36].**Hypertension had long been considered as leading risk for ICH and a predictor for poor outcome **[37, 38]** which highlighted the role of blood pressure control in improving prognosis in such cases **[39].**

In our work, there was an association between higher INR level and poor outcome of ICH, (P = 0.022). In agreement with our work, a study showed that there was significant increase in hematoma volume occurs with INR values that are greater than three **[40].**

In our study we found that higher NIHSS score indicated a poor outcome in ICH patients (P = 0.01). The NIHSS is a reliable tool for estimating stroke severity, and admission scores correlate well with post-ICH patient outcomes **[41-43].**

Our study did not find significant associations between poor outcome and several other variables, including age, gender, history of heart disease, diabetes. While these results may differ from some previous research, they highlight the complex and multifactorial nature of ICH outcomes, suggesting that individual patient characteristics and comorbidities may interact in different ways.

Our study was limited by several factors: First, being a leading cause of worldwide morbidity and mortality, sample size should be large with involvement of many centers. Another limitation is that we did not evaluate the preadmission or in hospital statin therapy and its effects on lipid profile. Also fractions of lipid were not determined.

Future large multicenter research considering the in hospital management of ICH and long term follow up should be considered.

Conclusion: ICH outcome is multifactorial involving different modifiable and unmodifiable factors. Hypertension, initial severity, bleeding tendency could predict outcome in addition to the lipid profile.

Conflicts of interest: None

Financial disclosures: None

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Citation:

Ismail, M., Khalil IbrahIm, G., Elaidy, S. Serum Biomarkers Predicting Prognosis of Spontaneous Intracerebral Hemorrhage. Zagazig University Medical Journal, 2024; (3298-3307): -. doi: 10.21608/zumj.2024.303983.3473