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Association of C-Reactive Protein Levels with the Severity of Spontaneous Intracerebral Hemorrhage

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ABSTRACT:

BACKGROUND:

Intracerebral hemorrhage (ICH) is a critical and debilitating form of stroke, affecting over one million people globally each year. Recent research has focused on exploring the role of C-reactive protein (CRP) in ICH cases.

OBJECTIVE:

This study aimed to investigate the association between CRP levels and the severity of spontaneous ICH.

PATIENTS AND METHODS:

A cross-sectional study was conducted at Al-Imamein Al-Kadhimein Medical City and Al-Yarmouk Teaching Hospital. It included patients aged 18 years or older with a primary diagnosis of ICH within 48 hours of symptom onset.

RESULTS:

A total of 107 patients with acute ICH were included. The majority (57%) were aged 46–65 years, with a mean age of 58.65 years. Males accounted for 66.4% of cases. Elevated CRP levels (>10 mg/L) were observed in 63.6% of patients, with a mean CRP of 37.32 mg/L. The average ICH score was 1.14, and most cases (37.4%) had an ICH score of 1. A Glasgow Coma Scale (GCS) range of 13–15 was most common, with a mean GCS of 12.95.

CONCLUSION:

CRP levels in ICH patients were not significantly correlated with GCS, ICH scores, or mortality risk, suggesting a limited role in acute severity.

KEYWORDS: CRP; intracerebral hemorrhage; severity.

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INTRODUCTION:

Intracerebral hemorrhage (ICH) is the second leading cause of stroke after ischemic stroke and contributes significantly to both disability and death. It can be classified as either spontaneous or trauma-induced [1]. ICH is more prevalent in Asian populations, older individuals, males, and low and middle-income nations [2]. The incidence of cerebrovascular accidents in Iraq has shown a notable rise, particularly following 2008 [3]. The mortality rate for ICH is significant (40% within the first month and 54% after one year), with only 12% to 39% of survivors managing to regain long-term functional independence [2].

While hypertension takes the lead as the most prevalent risk factor in ICH patients Increased blood pressure is linked to a greater likelihood of developing ICH, poorer prognosis following ICH, and, among survivors, a heightened risk of recurrence. [4], other contributors include apolipoprotein alleles E2 or E4, regular alcohol consumption, and cigarette smoking [5].

CRP serves as an indicator of both acute and chronic inflammation, potentially contributing to vascular damage in various cardiovascular diseases [6-7]. When faced with an acute-phase trigger, the levels of CRP in the bloodstream escalate rapidly, doubling every 6 hours. The plasma half-life of CRP is approximately 19 hours, and its peak concentrations are typically observed about 48 hours after exposure to a single stimulus [8].

Earlier research indicates a correlation between elevated CRP levels and unfavorable outcomes in conditions such as ischemic stroke [9], intracranial arterial stenosis [10], subarachnoid hemorrhage [11], and acute coronary artery diseases [12].

Nevertheless, there remains a research gap, as few studies have been dedicated to the prevention and treatment of ICH events, in contrast to ischemic stroke [13-14]. This study is crucial because, during the development of ICH, an inflammatory response is triggered by cerebral vessel hemorrhage, with CRP serving as a key indicator of this process. However, evidence linking CRP to ICH remains limited [15].

THE AIM OF THIS STUDY:

Is to investigate the relationship between CRP levels and the severity of spontaneous ICH, along with factors that may influence this relationship, in patients admitted to the neurological ward of Al-Imamain Al-Kadhimain Medical City and Al-Yarmouk Teaching Hospital.

PATIENTS AND METHODS:

In this hospital-based cross-sectional study, 107 patients were admitted to the Neurology Department of AL-Imamain Medical City and Al-Yarmouk Teaching Hospital. Patients were enrolled between January 2023 and October 2023.

Patients' selection criteria were as follows:

All patients with ICH symptoms who arrived at the hospital within 24 hours of onset, aged 18 years or older (both male and female), had a primary diagnosis of ICH based on history, clinical examination, and confirmation on neuroimaging with computed tomography (CT) of the brain, and were admitted either directly or through the emergency department.

Patients were excluded if they had a secondary ICH due to the following: hemorrhagic transformation of ischemic infarction, brain tumor, trauma, drug-induced causes, or other conditions.

In this investigation, we considered prevalent and easily modifiable risk factors, encompassed the identification of hypertension in patients with either primary or secondary hypertension, a history involving regular or irregular treatment, or determination of arterial blood pressure values ≥ 140/90 mmHg.

Diabetes mellitus was assessed through criteria such as fasting plasma glucose ≥126 mg/dL or a single value ≥200 mg/dL, along with a prior diagnosis and treatment history, and levels of HBA1C. Additionally, data on body mass index (BMI) were collected, defining overweight as BMI ≥25 Kg/m2 and obesity as BMI ≥30 Kg/m2. Participants were also scrutinized for dyslipidaemia, indicated by serum cholesterol exceeding 200 mg/dL, serum triglyceride levels surpassing 150 mg/dL, or the use of lipid-lowering drugs.

The initial Glasgow Coma Scale (GCS) and ICH score were recorded on admission. The ICH hematoma volume was evaluated using the ABC/2 method on the initial head CT scan. This method involves measuring the greatest diameter on the largest haemorrhage slice (A), the diameter perpendicular to A (B), and the approximate number of axial slices with haemorrhage multiplied by the slice thickness (C) [15].

In our study, we used the ICH score, GCS at admission, and the rate of in-hospital death to evaluate the severity of ICH. Patient data were gathered through direct interviews using a validated questionnaire specifically designed for this purpose. CRP categorization defined by the Centers for Disease Control and Prevention and the American Heart Association, CRP levels were classified into three groups: CRP <3 mg/l, CRP = 3–10 mg/l, and CRP >10 mg/l [16].

Ethical considerations:

Approval was obtained from the Neurology Scientific Committee of the Iraqi Board. An agreement for research was obtained from the authorities of the hospitals. Consent was obtained by all participants in this study.

Data handling and statistical analysis

Data were introduced into Microsoft Excel sheet 2019 and loaded into Statistical Package for Social Sciences version (24). Parametric data were presented as mean and standard deviation. Categorical data were presented as numbers and percentages. The chi-square test and Fisher exact test were used to test homogeneity. One-way ANOVA test measured the difference between groups' parametric variables. P-value < 0.05 was considered as significant.

RESULTS:

A total of **107 patients** with acute intracerebral haemorrhage (ICH) were enrolled within **48 hours** of symptom onset.

Demographic and Clinical Characteristics

The mean age was 58.65 ± 12.91 years (range: 22–87 years), with the highest proportion of patients 57.0% (n = 61) in the 46–65 years old age group. Males accounted for 66.4% (n = 71) of the study population. Regarding body mass index (BMI), 50.5% (n = 54) of patients were overweight, and 14.0% (n = 15) were obese, with a mean BMI of 25.98 ± 3.29 kg/m². Smoking was reported in 49.5% (n = 53) of patients, and 8.4% (n = 9) were alcohol consumers. Hypertension was the most prevalent comorbidity, affecting 93.5% (n = 100) of patients, followed by diabetes mellitus 38.3% (n = 41) and dyslipidaemia 44.9% (n = 48) (Table 1).

Table 1: **Demographic, Clinical Characteristics, and CRP Association of Study Sample.**

Characteristic	Total (N=107) Mean ± SD	CRP [a] < 3 mg/L (N=10) Mean ± SD	CRP 3-10 mg/L (N=27) Mean ± SD	CRP > 10 mg/L (N=70) Mean ± SD	P-value
Age Groups(years)	58.65 ± 12.91	64.33 ± 7.41	52.89 ± 11.07	59.94 ± 13.64	0.014
≤ 45 years	17 (15.9%)	1 (10.0%)	8 (29.6%)	8 (11.4%)	
46 – 65 years	61 (57.0%)	4 (40.0%)	10 (37.0%)	47 (67.1%)	
> 65 years	29 (27.1%)	5 (50.0%)	9 (33.3%)	15 (21.4%)	
Sex					0.763
Male	71 (66.4%)	9 (12.7%)	17 (23.9%)	45 (63.4%)	
Female	36 (33.6%)	3 (8.3%)	10 (27.8%)	23 (63.9%)	
BMI [b] (kg/m²)	25.98 ± 3.29	27.66 ± 2.74	26.40 ± 3.43	25.98 ± 3.23	0.082
Normal (18-24.9)	38 (35.5%)	2 (20.0%)	14 (51.9%)	22 (31.4%)	
Overweight (25-29.9)	54 (50.5%)	7 (70.0%)	11 (40.7%)	36 (51.4%)	
Obese (>30)	15 (14.0%)	1 (10.0%)	2 (7.4%)	12 (17.1%)	
Smoking					0.263
Yes	53 (49.5%)	5 (9.4%)	17 (32.1%)	31 (58.5%)	
No	54 (50.5%)	7 (13.0%)	10 (18.5%)	37 (68.5%)	
Alcoholism					0.585
Yes	9 (8.4%)	1 (11.1%)	1 (11.1%)	7 (77.8%)	
No	98 (91.6%)	11 (11.2%)	26 (26.5%)	61 (62.2%)	
Hypertension					0.475
Yes	100 (93.5%)	11 (11.0%)	24 (24.0%)	65 (65.0%)	
No	7 (6.5%)	1 (14.3%)	3 (42.9%)	3 (42.9%)	
Diabetes Mellitus					0.677
Yes	41 (38.3%)	6 (14.6%)	10 (24.4%)	25 (61.0%)	
No	66 (61.7%)	6 (9.1%)	17 (25.8%)	43 (65.2%)	
Dyslipidaemia					0.292
Yes	48 (44.9%)	7 (14.6%)	9 (18.8%)	32 (66.7%)	
No	59 (55.1%)	5 (8.5%)	18 (30.5%)	36 (61.0%)	

Notes: a CRP = C-reactive protein b BMI = Body Mass Index

ICH Severity and Inflammatory Markers

The highest proportion of cases had **C-reactive protein (CRP) > 10 mg/L (63.6%, n = 68)**, with a mean CRP of **37.32 ± 57.91 mg/L**. The mean ICH score at admission was **1.14 ± 1.03**, with most patients (**37.4%, n = 40**) having an ICH score of **1**.

The majority of patients (**74.8%, n = 80**) had a **Glasgow Coma Scale (GCS) score of 13–15**, with a mean GCS of **12.95 ± 3.24** (Table 3-2).

Table 2: **Clinical Findings of Study Participants.**

Characteristic	N (%)	Mean ± SD
CRP [a] levels		**37.32 ± 57.91 mg/L**
< 3 mg/L	12 (11.2%)	
3 – 10 mg/L	27 (25.2%)	
> 10 mg/L	68 (63.6%)	
ICH [b] Score		**1.14 ± 1.03**
0	33 (30.8%)	
1	40 (37.4%)	
2	23 (21.5%)	
3	8 (7.5%)	
4	3 (2.8%)	
GCS [c] Score		**12.95 ± 3.24**
3 - 4	3 (2.8%)	
5 - 12	24 (22.4%)	
13 - 15	80 (74.8%)	

Notes: a CRP = C-reactive protein b ICH = Intracerebral hemorrhage c GCS = Glasgow Coma Scale

Clinical Outcomes

The **survival rate with rehabilitation** was **81.0%**, while the **in-hospital mortality rate** was **19.0%** (Figure 1).

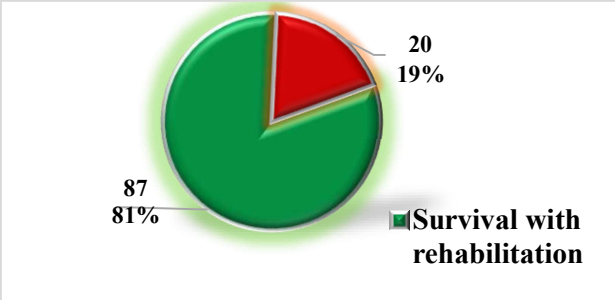

Figure 1: Clinical Outcomes of ICH Patients.

There was **no significant association** between **CRP levels and in-hospital mortality (P = 0.584)** (Table 3).

Table 3: Association Between CRP Levels and In-Hospital Outcomes.

CRP Level	Survival with Rehabilitation	In-Hospital Death	P-value
< 3 mg/L	11 (91.7%)	1 (8.3%)	**0.584**
3 - 10 mg/L	21 (77.8%)	6 (22.2%)	
> 10 mg/L	55 (80.9%)	13 (19.1%)	

Figure 2 illustrates the distribution of **CRP levels across different ICH scores**, showing that most patients with **CRP < 3 mg/L had an ICH score of 0 or 1**.

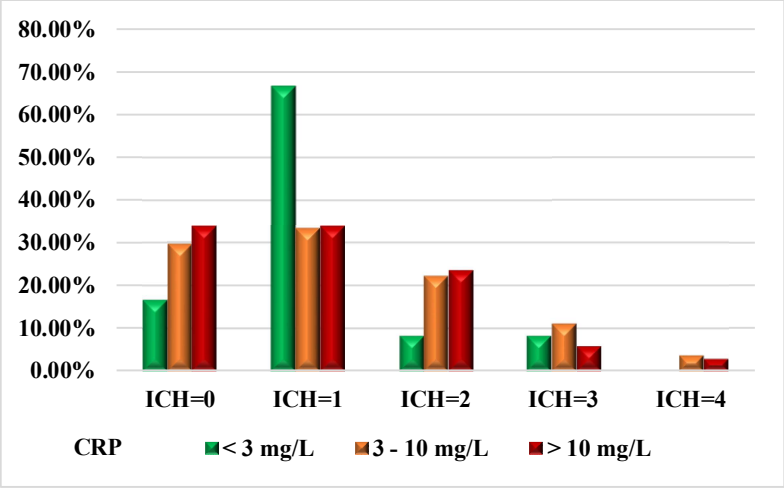

Figure 2: The distribution of CRP (C-reactive protein) level proportions with the ICH (Intracerebral hemorrhage) score.

Figure 3 depicts the **distribution of CRP levels among GCS categories**, indicating that patients with **CRP < 3 mg/L** were predominantly in the **GCS 13-15 group**.

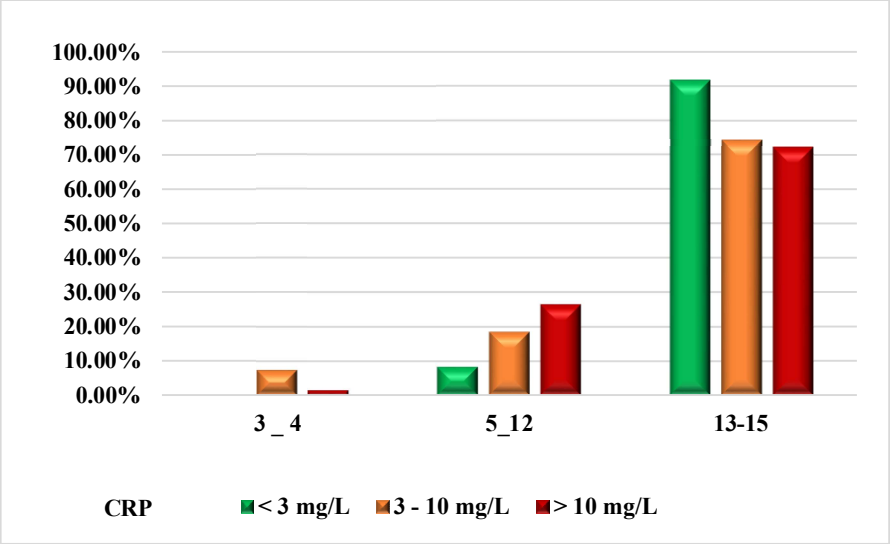

Figure 3: The distribution of CRP level proportions with the GCS (Glasgow Coma Scale)

DISCUSSION:

The study used the ICH score, GCS upon admission, and in-hospital mortality to evaluate ICH severity. Findings showed no significant association between CRP levels and initial GCS (p=0.485) or ICH score (p=0.788). However, lower CRP levels (<3 mg/L) were more common in patients with milder ICH scores (0–1) and higher GCS scores (13–15). While no patients had an ICH score of 6, the lack of survivors among those with a score of 5 suggests a high mortality risk for a score of 6. [17]. CRP levels (3–10 mg/L and >10 mg/L) did not significantly predict mortality (p=0.584), aligning with Borowicz's and Bernstein's findings that CRP has no distinct impact on haemorrhagic stroke or ICH mortality [9], [18]. However, contrasting research by Wang suggests that elevated CRP levels are linked to poorer outcomes and higher in-hospital mortality in ICH patients [19].

The study found that 57.0% of ICH patients were aged 46–65, reinforcing the established link between advancing age and increased ICH incidence [20], [21]. A significant variation (p=0.014) in CRP levels was observed across age groups, with lower CRP levels (<3 mg/L) more common in older patients (64.33±7.41 years) compared to those with moderate (52.89±11.07 years) and high CRP levels (59.94±13.64 years). Additionally, ICH was more prevalent in males (66.4%) than females (33.6%), consistent with previous research [20]. However, no significant association (p=0.763) was found between gender and CRP levels, and it remains unclear whether this male predominance is due to equal exposure to risk factors or underlying genetic influences [22].

Baseline clinical data for our study also shows that 64.5% of patients had a BMI >25 kg/m², but no significant correlation was observed between BMI and CRP levels (p=0.082), differing from prior research linking obesity to elevated CRP [23], [24], this discrepancy may stem from BMI's limitations in assessing body fat, as women generally have higher fat percentages at the same BMI [25].

Smoking, despite being a known cerebrovascular risk factor, also showed no significant association with CRP (p=0.263), possibly due to underreporting or sample size limitations. Similarly, alcohol consumption, reported by only 8.4% of patients—likely influenced by cultural factors—did not show a significant correlation with CRP levels (p=0.585).

Hypertension was prevalent in 93.5% of patients, consistent with previous studies reporting rates between 40% and 84% [26], [27], with variations likely due to differences in hypertension management across countries. Diabetes (38.3%) and dyslipidaemia (44.9%) were less common but have been linked to higher ICH mortality in prior research [28], [29], despite the known associations between these conditions and ICH, no significant correlation was found between CRP levels and hypertension, diabetes, or dyslipidaemia.

Limitations.

This study is limited by a small, region-specific sample, lack of a control group, and the inability to assess functional outcomes due to ICH score constraints.

CONCLUSIONS & RECOMMENDATIONS:

CRP levels in ICH patients showed no significant correlation with GCS, ICH score, or mortality prediction, indicating a limited role in acute-phase severity.

Recommendation:

Evaluating the ICH score 24-hour post-onset provides a more accurate prognosis by considering dynamic changes in GCS, IVH, and hematoma volume influenced by treatment.

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Author contribution: all authors contributed equally to this study.

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