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# Assessment of Blood Count Abnormalities in Relation to Clinical outcome of Intracerebral Hemorrhage

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**ABSTRACT**

Spontaneous non-traumatic intracerebral hemorrhage (ICH) constitutes about 10–15% of all strokes and has a high mortality of approximately 40% at 1 month. Identifying the factors associated with mortality may improve survival rate and avert patients many complications. To evaluate the routine blood count finding in ICH patient, in relation to with clinical outcome. This is a case series prospective study included 60 patients who presented with diagnosis of ICH. Clinical data, and laboratory investigations were gathered from patient's records. Radiological parameter was also registered with aid of expert neurologist looking for site and size of bleeding. Fate of the patient was monitored according to neurologist opinion and categorized as complete recovery, or death within first 30 days of presentation. Outcomes were defined within 30 days of presentation and revealed that 13 patients (21.67%) died. The site of hemorrhage was Intraventricular hemorrhage (IVH) in 61.54% of non-survived patients compared with 23.40% among survived patients with a highly significant difference (p= 0.009). Mean hemoglobin (Hb) concentration in survived patients was 13.58±1.83 g/dl, which was s higher than that of non-survival patients (12.03±1.52 g/dl) with a highly significant difference (*p*= 0.007). In contrast, mean platelet lymphocyte ratio (PLR) in non-survived patients was 271.89±113.93 which was significantly higher than that of survived patients (214.97±140.11) (*p*= 0.033). Hb level (< 12.85 g/dl) and high PLR (> 249%) may predict high mortality rate in patients with ICH.



## 1. Introduction

Intracerebral hemorrhage (ICH) is usually caused by rupture of small penetrating arteries secondary to hypertensive changes or other vascular abnormalities [1- 3]. In developed countries, the incidence of hypertensive ICH has decreased with the improvement of blood pressure control. However, in developing countries, the burden of ICH has not decreased [1]. The outcome of ICH is variable, depending on hematoma volume, location, extension to ventricles, and other factors. However, compared to ischemic stroke, ICH leads to higher mortality and more severe disability [2].

For all ages, the annual incidence rate per 100,000 persons was higher in men than in women [4]. The incidence rates of primary ICH in low- and middle-income countries were twice the rates in high-income countries (22 vs. 10 per 100,000 person-years) [5].

Hypertension, smoking, waist-to-hip ratio, diet, and high alcohol intake were major risk factors for ICH, and these modifiable risk factors accounted for 88.1% of the population-attributable risk [6].

Anticoagulation-related ICH is nowadays [7], as well as Dual antiplatelet therapy related had reported significantly [8].

Hypertension-related ICH often occurs at deep sites in the brain where small, thin-walled arteries comedirectly off of larger arteries (basal ganglia, thalamus, cerebellum, and brainstem, especially the pons) [9].

ICH is associated with significant morbidity and mortality, the most widely used tool for assessing prognosis is (ICH score) a scale that predicts mortality based on hemorrhage size, patient age, Glasgow coma score, hemorrhagelocation (infratentorial or supratentorial), and the presence of intraventricular hemorrhage [10].

Concerning the impact of anemia on ICH outcome is rather uncertain, many studies have indicated that low hemoglobin level may be associated the poor outcome in patients with ICH [11], [12]. Although the mechanisms underlying the association between anemia and poorer outcome in ICH was still unknown, several studies suggested the correlation of anemia and abnormal coagulation, hemostatic alterations, and an increased bleeding tendency [13].

Aim of study is to evaluate the routine blood count finding in ICH patient, in relation to with clinical outcome.

## 2. Patients and Method

### *2.1 Settings and Design*

This is a case series prospective study which is conducted at Al-Imamain Al-Kadhumain Medical City from February 2020 to January 2021.

The study was approved by the ethical committee of Iraqi Council of Medical Specialization.

It included 60 patients who presented with clinical signs and symptoms of hemorrhagic stroke as ICH based on presentation and proved by brain CT scan on day 0 of presentation and hospital admission.

Some patients were Excluded like those with delayed presentation> 24 h after ICH or having an underlying hematologic disorders or using anticoagulants, in addition to patient with acute ICH due to trauma, space occupying lesion or using immunosuppressant drug and steroids. Other excluded were those with a history of infection within 2 weeks before ICH, or recurrent stroke history within 6 months. A verbal consent from each participant was obtained prior to data collection. The confidentiality of data throughout the study was guaranteed and the patients were assured that data will be used for research purpose only.

### *2.2 Data collection*

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For each eligible patient, data were collected like demographic parameters, past medical history for risk factors for ICH (Hypertension, etc..), clinical features (onset, manifestation, like headache, coma, paralysis etc…), and laboratory investigations (including Hb, PCV, RBC indices, WBC count as well as platelet).

Radiological features were also registered according to expert neurologist opinion and radiology report looking for site and size of bleeding. Fate was determined and categorized as complete recovery, or death within first 30 days of presentation.

Hypertension was defined using the 2013 ESH/ESC Guidelines: resting systolic pressure (SBP) at ≥ 140 mmHg and/or diastolic pressure (DBP) at≥90 mmHg on three separate occasions or regular use of antihypertensionmedications [14].

All laboratory tests were carried out using venous blood collected after over-night fasting.

All automated blood count where assessed by hospital central lab using Hematology auto-analyzer (Huroba ABX/India).

## 3. Results

The mean age of the patients was 58.48±15.08 years (range 23-91 years), about three-fourth (73.33%) of them were males. Smokers represent 41.67% of the patients. Within the first 30 days of presentation, 13 patients (21.67%) died and 47 patients (78.33%) survived.

### *3.1 Clinical Characteristics of the Patients*

The majority of patients (80%) presented with unilateral weakness (whether right or left sided). Decreased level of conscious (DLOC) was the second most common presentation encountered in 25% of the patients followed by headache (18.33%) and seizure (15%). Radiologically, the most common site of the hemorrhage was deep seated (60%) followed IVH (31.67%).

With the exception of 5 patients, all patients presented with one or more comorbidity. Hypertension (HTN) was reported in all comorbid patients. Other comorbidities included T2DM and IHD, each of which encountered in 34.55% and of the comorbid patients (Table 1).

### *3.2 Hematological Parameters of the Patients*

The mean Hb concentration was 13.25±1.87 g/dl with mean MCV of 83.84±6.65 ft. The mean total WBC count was 11.26±3.93 ×103/ml which consistent neutrophilia (mean= 9.26±3.7×$10_3$/ml).

In most patients, platelets were within normal range with an average of 248.02±82.06 ×$10_3$/ml. There were high ratios for both NLR and PLR (mean =9.37±7.37 and 227.3±136.03, respectively) (Table 2).

### *3.3 Association of Demographic and Clinical Characteristics with Outcome*

None of the demographic characteristics or comorbidities showed a significant association with the survival rate. In contrast, clinical presentation and hemorrhage site do have. DLOC was presented in 46.15% and 19.15%, respectively in non-survived and survived patients with a significant difference ($p$= 0.047). Likewise, the site of hemorrhage was IVH in 61.54% of non-survived patients compared with 23.40 among survived patients with a highly significant difference ($p$= 0.009) (Table 3).

### *3.4 Association of Hematologic parameters with the Patients' Outcome*

Only two hematologic parameters showed a significant association with the survival rate. Mean Hb concentration in survived patients was 13.58±1.83 g/dl, which was s higher than that of non-survival patients (12.03±1.52 g/dl) with a highly significant difference ($p$= 0.007). In contrast, mean PLR in non-survived patients was 271.89±113.93 which was significantly higher than that of survived patients (214.97±140.11) ($p$= 0.033). Although neutrophil, platelet count and NLR were remarkably higher in non-survived than survived patients, the differences were not significant ($p$= 0.134,0.063,0.220 respectively) (Table 4).

### *3.5 Prognostic Value of Hb and PLR*

Receiver operating characteristic (ROC) curve was used to determine the cut-off values of each of Hb and PLR ratio. For Hb, the area under the curve (AUC) was 0.732, 95%CI=0.695-0.858, $p$=0.011. The sensitivity and specificity of the test at cut off value of Hb= 12.85 g/dl were 0.64 and 0.77respectively while for PLR, the AUC was 0.714, 95%CI=0.57-0.858, $p$=0.017. The sensitivity and specificity of the test at cut off value of PLR= 249% were 0.62 and 0.72 respectively

Kaplan-Meier survival curve was constructed to find out the prognostic value of Hb, PLR in overall survival (OS). Mean OS for patients with Hb ≤ 12.85 g/ml was 4.72 days (95%CI= 3.2-8.12), compared with over 30 days OS in patients with Hb > 12.85 g/dl with significant difference ($p$ = 0.007) (Figure 1).

Likewise mean OS for patients with PLR> 249was 4.72 days (95%CI= 3.2-8.12) compared with over 30 days OS in patients with PLR≤ 249with significant difference (p = 0.018) (Figure 2)

## 4. Discussion

Spontaneous ICH remains an important and frequent medical emergency, often with severe and devastating consequences for the patient. This study showed the mortality rate of 21.67% within the first 4 weeks of presentation. In different studies worldwide, the 30-day mortality of patients with spontaneous ICH has been reported as ranging from 25 to 52% [15], [16]. The relatively low rate in the present study might be explained by exclusion criteria applied for the eligible patients.

The main hematologic features that found to be associated significantly with patient outcome is Hb concentration as cut off of 12.85 was suggested in statistical term to be a land mark between those none survived in comparison with survived patient (p=0.009), in contrast to the association found with PLR which considered that a level higher than 249% can be attributed with early poor outcome in term of death. This is in accordance with others. [17] demonstrated that the overall short-term-survival was worse in anemic suggesting volume-undriven outcome-effects of anemia. Multivariate regression analyses revealed that anemia, besides established parameters, has the strongest relation to unfavorable outcome. This is even more pronounced in minor-volume-ICH.

Similarly, In a meta-analysis including 7 cohorts with 7328 ICH patients, of whom 1546 patients with anemia, [18] revealed that anemia at admission was associated with higher mortality (OR = 1.72 for 30-day mortality, 95% CI 1.37 to 2.15) and an increased risk of poor outcome in patients with ICH (OR = 2.29 for 3-month outcome, 95% CI 1.16 to 4.51).

It is assumed that the disturbed hemostasis in anemia was associated with abnormal vascular modulation since erythrocyte and hemoglobin could act as vascular modulator via activating endothelium-derived vasoconstriction [19].

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Other have been proposed that tissue hypoxia secondary to anemia will activate compensatory physiological mechanisms to increase Cerebral blood flow (CBF) and counteract reductions in Hb or subsequent reductions in cerebral delivery of O2 (DO2), in response to anemia [20]. Furthermore, dilation of cerebral arterioles (i.e. cerebral vasodilation) occurs because of an increased production of nitric oxide (NO) by endothelial cells, perivascular astrocytes, and neurons to improve CBF and preserve O2 delivery [21], [22].

The present study is one of very few studies that addressed the value of PLR in predicting ICH. Most previous studies investigated other pathologies.

[23] reported that high PLR level (>260 vs. <260) was an independent predictor of venous thromboembolism in patients with cancer, and [24] found that high PLR (>151 vs. <151) was associated with increased long-term major adverse cardiovascular events in patients with myocardial infarction.

Studies have confirmed that platelets play a critical role in immunomodulatory and inflammatory processes by inducing the release of inflammatory cytokines [25], [26] and interacting with various cells, including neutrophils, T lymphocytes, and macrophage, which contribute to the initiation or exacerbation of the inflammatory process [27]. Thus, high PLR may reflect the aggravated release of cytokines and increased thrombocyte activation, which lead to devastating inflammatory response. The lower circulating lymphocyte in circulation will make a relatively higher platelet in circulation than can be attributed to induce local hyepercoagulabilities inside microcirculation in presence with underlying physiologic vasoconcentration in cerebral circulatory bed with subsequent complications. It was also reported that in patients with ICH, high PLT can predict elevated perihematomal edema and is associated with poor discharge outcome [28].

Alternatively, high PLR, implies a relatively low lymphocyte count. Lymphocytopenia has been described in the context of stroke-induced immunosuppression syndrome, which usually is accompanied with monocyte dysfunction [29]. Many reports indicate that lymphocytopenia is a common feature in patients with ICH and is related both to increased rates of infection and to unfavorable outcome [30].

In Conclusions; it can suggested that Hb (< 12.85 g/dl) and high PLR (> 249%) can predict high early mortality rate in patients with ICH, while Neither age of the ICH patient nor his/her gender had shown any significance with outcome.

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**Table 1:** Clinical Characteristics of the patients (n=60)

| Variables | Frequency | percentage |
|---|---|---|
| **†Clinical presentation** | | |
| Unilateral weakness | 48 | 80% |
| DLOC | 15 | 25% |
| Headache | 11 | 18.33% |
| Seizure | 9 | 15% |
| Aphasia | 5 | 8.33% |
| Sensory loss | 4 | 6.67% |

| | | |
|---|---|---|
| ‡Others | 11 | 18.33% |
| **Site of hemorrhage** | | |
| Deep seated | 36 | 60% |
| IVH | 19 | 31.67% |
| Cortical | 10 | 16.67% |
| Cerbellar | 9 | 15% |
| **Comorbidities** | | |
| Present | 55 | 91.67% |
| HTN | 55 | 100% |
| DM with HTN | 19 | 34.55% |
| IHD with HTN | 19 | 34.55% |
| Absent | 5 | 8.33% |

†A patient can have more than one clinical presentation, site of hemorrhage or comorbidities.
‡Other presentations include facial palsy, sudden loss of conscious, motor and sensory disturbance and homonomus hemianopia. DLOC: Decreased level of conscious, HTN: hypertension, DM: diabetes mellitus, IHD: ischemic heart disease

**Table 2:** Hematological characteristics of the patients

| Variables | Value |
|---|---|
| **Hemoglobin, g/dl** | |
| Mean±SD | 13.25±1.87 |
| Range | 8.2-17.1 |
| **MCV, fl** | |
| Mean±SD | 83.84±6.65 |
| Range | 65.6-102.8 |
| **WBC count×$10^3$/ml** | |
| Mean±SD | 11.26±3.93 |
| Range | 4.5-25.3 |
| **Neutrophil count×$10^3$/ml** | |
| Mean±SD | 9.26±3.7 |
| Range | 2.77-22.91 |
| **Lymphocyte count×$10^3$/ml** | |
| Mean±SD | 1.431±1.27 |
| Range | 0.29-9.8 |
| **Platelets count×$10^3$/ml** | |
| Mean±SD | 248.02±82.06 |
| Range | 87-478 |
| **NLR, %** | |
| Mean±SD | 9.37±7.37 |
| Range | 1.31-36.6 |
| **PLR, %** | |
| Mean±SD | 227.3±136.03 |

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Volume 62, Issue 10, December, 2022

| | |
|---|---|
| Range | 16.41-623.53 |

MCV: mean corpuscular volume, NLR: neutrophil-lymphocyte ratio, PLR: platelet-lymphocyte ratio

**Table 3:** Association of demographic and clinical characteristics with the patients' outcome

| **Variables** | **Survived (n=47)** | **Non-survival (n=13)** | **p-value** |
|---|---|---|---|
| **Age, years** | 58.94±13.89 | 56.85±19.37 | 0.664 |
| **Sex** | | | |
| Male | 36(76.60%) | 8(61.54%) | 0.277 |
| Female | 11(23.40%) | 5(38.46%) | |
| **Smoking** | | | |
| No | 28(59.57%) | 7(53.85%) | 0.711 |
| Yes | 19(40.43%) | 6(46.15%) | |
| **Clinical presentation** | | | |
| Weakness | 39(82.98%) | 9(69.23%) | 0.273 |
| DLOC | 9(19.15%) | 6(46.15%) | **0.047** |
| Headache | 9(19.15%) | 2(15.38) | 0.756 |
| Seizure | 5(10.64%) | 4(30.77%) | 0.072 |
| Aphasia | 5(10.64%) | 0(0%) | 0.219 |
| Sensory loss | 4(8.51%) | 0(0%) | 0.276 |
| Others | 8(17.02) | 3(23.08%) | 0.617 |
| **Site of hemorrhage** | | | |
| Deep seated | 28(59.57%) | 8(61.54%) | 0.898 |
| IVH | 11(23.40%) | 8(61.54%) | **0.009** |
| Cortical | 9(19.15%) | 1(7.69%) | 0.327 |
| Cerebellar | 6(12.77%) | 3(23.08%) | 0.357 |
| **Comorbidities** | | | |
| Present | 43(91.49%) | 12(92.31%) | 0.925 |
| HTN | 43(91.49%) | 12(92.31%) | 0.925 |
| DM with HTN | 16(34.04%) | 3(23.08%) | 0.522 |
| IHD with HTN | 14(29.79%) | 5(38.46%) | 0.452 |
| Absent | 4(14.29%) | 1(7.69%) | 0.925 |

DLOC: Decreased level of conscious, IVH: Intraventricular hemorrhage, HTN: hypertension, DM: diabetes mellitus

**Table 4:** Association of hematologic parameters with the patients' outcome

| **Variables (mean±SD)** | **Survived (n=47)** | **Non-survival (n=13)** | **p-value** |
|---|---|---|---|
| Hemoglobin, g/dl | 13.58±1.83 | 12.03±1.52 | **0.007** |
| MCV, fl | 84.62±5.42 | 81.03±9.38 | 0.081 |

| | | | |
|---|---|---|---|
| WBC count×$10^3$/ml | 10.88±3.82 | 12.62±4.18 | 0.160 |
| Neutrophil count×$10^3$/ml | 8.88±3.66 | 10.63±3.68 | 0.134 |
| Lymphocyte count×$10^3$/ml | 1.5±1.4 | 1.27±0.57 | 0.562 |
| Platelets count×$10^3$/ml | 237.68±72.76 | 285.38±104.36 | 0.063 |
| NLR, % | 8.76±7.36 | 11.61±7.36 | 0.220† |
| PLR, % | 214.97±140.11 | 271.89±113.93 | **0.033†** |

† Mann Whitney U test, MCV: mean corpuscular volume, WBC: while blood cells, NLR: neutrophil-lymphocyte ration

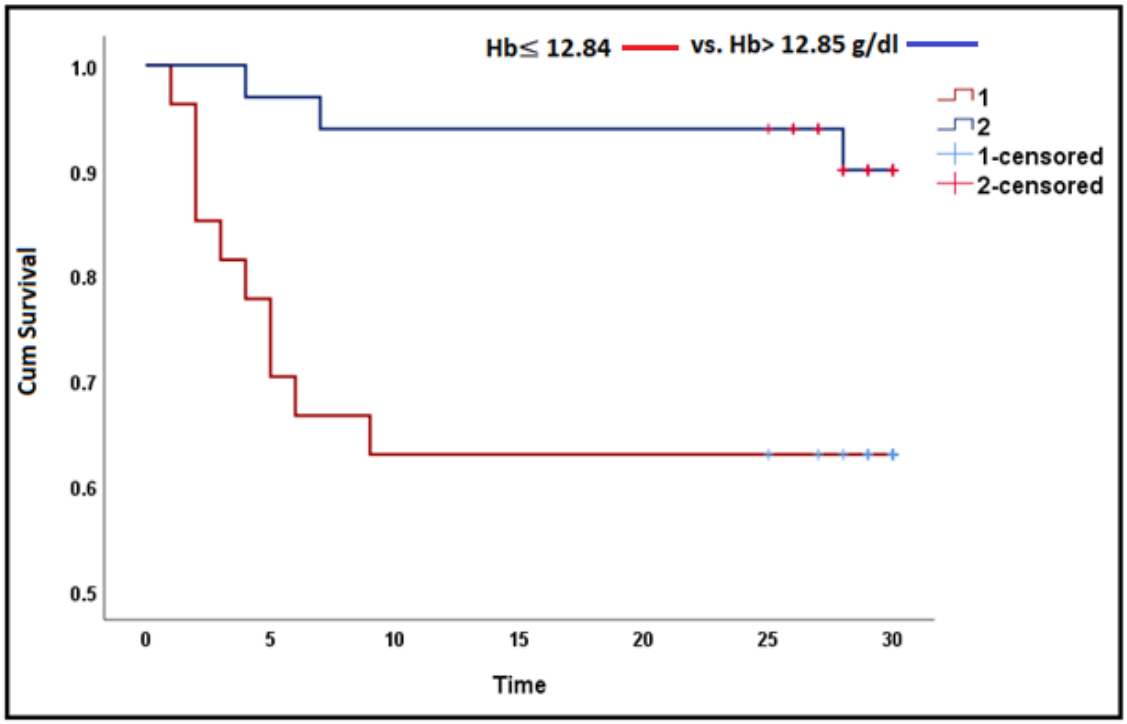


**Figure 1:** Kaplan-Meier curve. Mean time for survival Hb ratio ≤ 12.85 g/dl was 4.72 days compared with over 30 days survival in patients with Hb>12.85 g/dl, p= 0.007

ISSN: 0005-2523
Volume 62, Issue 10, December, 2022

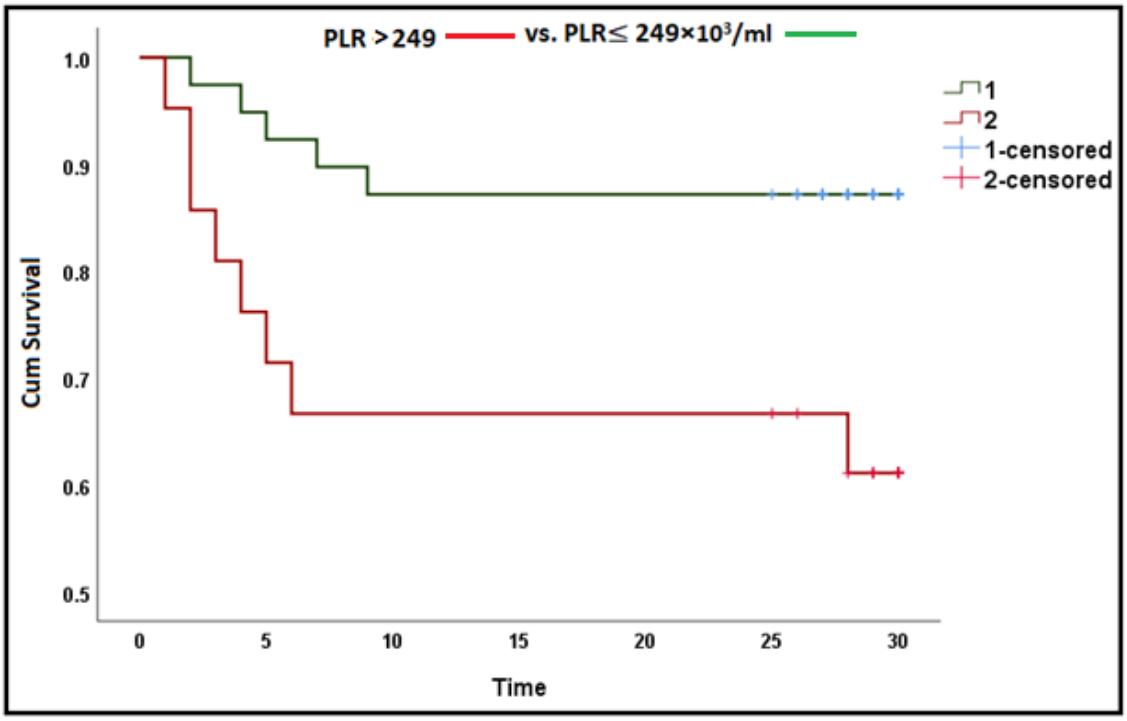


**Figure 2:** Kaplan-Meier curve. Mean time for survival PLR> 249was 4.72 days compared with over 30 days survival in patients with PLR≤ 249, p= 0.018.