Am J Transl Res 2025;17(11):8693-8699
www.ajtr.org /ISSN:1943-8141/AJTR0164019

*Original Article*

# Relationship between blood inflammatory indices and prognosis in patients with intracerebral hemorrhage

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Received February 18, 2025; Accepted October 23, 2025; Epub November 15, 2025; Published November 30, 2025

**Abstract:** Objectives: The neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and platelet-to-lymphocyte ratio (PLR) are biomarkers of inflammation and immune status. We aimed to investigate the relationship between NLR, MLR, PLR, and atherogenic index of plasma (AIP) levels and prognosis in patients with intracerebral hemorrhage (ICH). Methods: In total, 176 patients with ICH were retrospectively enrolled in this clinical study. Admission blood cell counts were used for the analysis via the hospital automation system. Patients were divided into subgroups according to the hemorrhage type (IPH and SAH), the treatment method (conservative and surgical), and the mortality rates within 48 hours, at 1 month, and 3 months. Blood indices were compared between these subgroups. Results: The median age was 68 years (56-77), and 108 patients (61.4%) were men. IPH was observed in 154 patients (87.5%), and SAH was present in 22 patients (12.5%). The NLR, MLR, PLR, and AIP values were significantly elevated in IPH patients over those with SAH ($P < 0.05$); these blood parameter values did not significantly differ between patients who received surgical (8.5%) versus medical (91.5%) treatment. Similarly, these values did not significantly differ between mortality subgroups ($P > 0.05$). Conclusion: NLR, MLR, PLR, and AIP values were not associated with prognosis in patients with ICH, a result which does not yet support the use of these markers for short-term risk prediction. Larger cohorts with longitudinal follow-up are needed.

**Keywords:** Neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, platelet-to-lymphocyte ratio, atherogenic index of plasma, intracerebral hemorrhage

## Introduction

Hemorrhagic strokes constitute 10-20% of all strokes [1]. Intracerebral hemorrhage (ICH) is associated with high mortality and morbidity despite advances in medical intensive care and neurosurgical interventions [2]. At one year, the mortality rate approaches 54%, and among those who survive, only 12-39% achieve long-term functional independence [2].

Recent studies have shown a significant correlation between elevated inflammatory markers and an increased likelihood of hemorrhagic transformation in cases with ischemic stroke [3-6]. Whether these ratios are also important in hemorrhagic stroke remains unclear. The majority of ICH subjects result from hypertension, which is closely related to arterial stiffness in the pathophysiology of atherosclerosis [7]. Chronic high blood pressure can lead to arterial wall damage through oxidative stress and increased inflammation. Therefore, we hypothesized that inflammatory ratios are also involved in ICH.

The neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and platelet-to-lymphocyte ratio (PLR) are biomarkers of inflammation and immune status and have become the focus of clinical attention [4, 8]. Several reports have demonstrated that a high value of NLR upon admission is linked to unfavorable prognosis in subjects with spontaneous ICH [9-12]. Jiang et al. reported that MLR at admission is significantly associated with high in-hospital mortality in cases with hemorrhagic stroke [13]. Similarly, the PLR represents both aggregation and inflammatory pathways [14]. PLR value was found to predict the possi-

https://doi.org/10.62347/NLHI2912

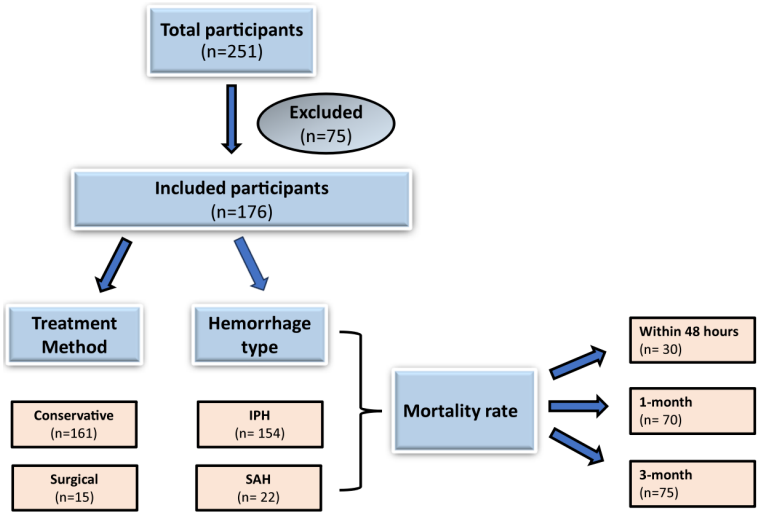


**Figure 1.** Flow diagram of the study. SAH: Subarachnoid hemorrhage, IPH: Intraparenchymal hemorrhage, NLR: Neutrophil-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, AIP: Atherogenic index of plasma.

bility of hemorrhagic transformation, a severe complication of ischemic stroke [5, 6, 15]. However, no data are available on the role of PLR in ICH patients. The atherogenic index of plasma (AIP) has emerged as a potential novel indicator of plasma atherogenicity [16]. It is calculated as the logarithm of the molar ratio between serum triglyceride levels and high-density lipoprotein cholesterol [17]. To date, no study has investigated AIP in patients with ICH.

Limited data have focused on a single marker in patients with hemorrhagic stroke. We aimed to investigate the relationship between NLR, MLR, PLR, and AIP levels and prognosis in patients with ICH.

## Methods

*Study design*

This retrospective study included the medical records of 176 patients diagnosed with ICH who were admitted to the emergency department of Kirsehir Training and Research Hospital (Kirsehir, Turkey) between September 2019 and 2023. Ethical approval was obtained from the Local Research Ethics Committee of Kirsehir Ahi Evran University (approval date: 10/24/2023; approval number: 2023-18/136).

Patients over the age of 18 who were diagnosed with ICH based on a computed tomography scan of the brain were involved in the present study. The patients were grouped as intraparenchymal hemorrhage (IPH) and subarachnoid hemorrhage (SAH). Patients meeting the following criteria were selected for surgical intervention: progressive impairment of consciousness; cerebral hematomas exceeding 15 $cm^3$ in volume, cerebellar hematomas larger than 3 cm in diameter; evidence of brainstem compression or midline shift; potential for obstructive hydrocephalus; presence of lobar, external capsule, or cerebellar hematomas; and hematomas localized in the non-dominant hemisphere. Medical management was administered to patients presenting with small hematomas, either minor or significant neurological deficits, deep-seated hemorrhages (such as those in the basal ganglia or pons), and elderly patients (> 75 years) who were deemed unsuitable for surgical intervention [18].

Patients with acute ischemic stroke and/or those with secondary hemorrhagic transformation, secondary tumor bleeding, and hematological diseases that may cause abnormalities in blood counts - such as liver cirrhosis, myelodysplastic syndrome, myelofibrosis, leukemia, aplastic anemia, neutropenia after chemotherapy, steroid use, pregnancy, or a history of local trauma or surgery - were excluded. Patients with incomplete data were also eliminated from the analysis.

Data have shown high levels of peripheral inflammatory biomarkers in ischemic stroke. We hypothesized that these ratios, all of which were related to inflammation, might also be elevated in hemorrhagic stroke including similar underlying mechanisms [19]. Thus, we aimed to investigate the blood inflammatory indices - such as NLR, MLR, PLR, and AIP - in relation with short-term prognosis in patients with ICH. As shown in a flow diagram (**Figure 1**), the data of 251 patients were analyzed retrospectively, and 75 patients were excluded based on the exclusion criteria. Finally, 176 of them were included in this study. Demographic

**Table 1.** Demographic data and baseline clinical characteristics in patients with intracerebral hemorrhage (n = 176)

| Variables | |
|---|---|
| Age (years) | *68 (56-77)* |
| Male gender | *108 (61.4)* |
| COMORBIDITIES | |
| Hypertension | *85 (48.3)* |
| Diabetes mellitus | *39 (22.2)* |
| Coronary artery disease | *23 (13.1)* |
| Chronic kidney disease | *13 (7.4)* |
| Atrial fibrillation | *12 (6.8)* |
| Congestive heart failure | *9 (5.1)* |
| Parkinson's disease | *8 (4.5)* |
| Dementia | *8 (4.5)* |
| Chronic obstructive pulmonary disease | *3 (1.7)* |
| Epilepsy | *3 (1.7)* |
| MEDICATION | |
| Antihypertensives | *83 (47.2)* |
| Antithrombotics | *40 (22.7)* |
| Oral antidiabetics | *38 (21.6)* |
| Diuretics | *7 (4)* |
| Antiepileptics | *2 (1.1)* |
| Inhaler bronchodilators | *3 (1.7)* |
| HEMORRHAGE TYPE | |
| Intraparenchymal hemorrhage | *154 (87.5)* |
| Subarachnoid hemorrhage | *22 (12.5)* |
| TREATMENT METHOD | |
| Conservative | *161 (91.5)* |
| Surgical | *15 (8.5)* |
| MORTALITY RATE | |
| Within 48 hours | *30 (17)* |
| 1-month | *70 (39.8)* |
| 3-month | *75 (42.6)* |

Values are expressed as n (%) or median (IQR 25-75).

data included age, sex, comorbidities, and medications. Routine hematological and biochemical analyses were performed in our laboratory. The admission differential count was utilized to compute the laboratory inflammatory ratios, including NLR, MLR, and PLR. The lipid profile obtained within the first 24 h of admission was included to calculate the AIP. The included patients were divided into subgroups according to the hemorrhage type (IPH and SAH) and the treatment method (conservative and surgical). Blood indices were compared between these subgroups. In addition, the mortality rates were calculated within 48 hours, at 1 month, and 3 months, and blood ratios were compared between surviving and deceased subgroups.

*Statistical analysis*

Histograms and Q-Q plots were examined, and the Kolmogorov-Smirnov test was performed to assess data normality. The data are presented as frequencies (n) and percentages (%), means with standard deviations, or medians along with interquartile ranges. The chi-square test was employed to assess the relationships between categorical variables. The independent samples t-test was applied to parameters with a normal distribution, while the Mann-Whitney U test was used for parameters that did not show a normal distribution. A p-value of less than 0.05 was regarded as indicative of statistical significance.

## Results

A total of 176 patients diagnosed with ICH were enrolled in this study. The baseline demographic and clinical characteristics of these patients are presented in **Table 1**. The median age was 68 years (56-77), with a male predominance (61.4%). The observed comorbidities included, in descending order, hypertension (48.3%), diabetes mellitus (22.2%), coronary artery disease (13.1%), chronic kidney disease (7.4%), atrial fibrillation (6.8%), congestive heart failure (5.1%), Parkinson's disease (4.5%), dementia (4.5%), chronic obstructive pulmonary disease (1.7%), and epilepsy (1.7%). The used medications were, in descending order, antihypertensives (47.2%), antithrombotics (22.7%), oral antidiabetics (21.6%), diuretics (4), antiepileptics (1.1%), and inhaler bronchodilators (1.7%). Of the 176 patients, 154 (87.5%) had IPH and 22 (12.5%) had SAH. A total of 161 (91.5%) patients were treated conservatively, while 15 (8.5%) were treated surgically. The mortality rate was 30 (17%) with-

**Table 2.** Comparison of laboratory parameters in patients with intracerebral hemorrhage (*n* = 176)

| | SAH (*n* = 22) | IPH (*n* = 154) | *P* |
|---|---|---|---|
| HDL (mg/dL) | 62 (56-80) | 41 (36-49) | *<0.001* |
| LDL (mg/dL) | 107 (80-121) | 105.5 (76-129) | *0.375* |
| Triglyceride (mg/dL) | 100 (88-118) | 123.5 (88-162) | *0.812* |
| Total cholesterol (mg/dL) | 150 (110-217) | 173.5 (148.6-198) | *0.171* |
| NLR | 1.8 (1.2-4.64) | 3.5 (1.9-7.9) | *0.010* |
| MLR | 0.2 (0.2-0.3) | 0.3 (0.3-0.5) | *0.004* |
| PLR | 83.7 (49.9-141.8) | 124.7 (91.8-214.9) | *0.008* |
| AIP | 0.2 (0.1-0.2) | 0.5 (0.3-0.6) | *0.002* |

Values are expressed as median (IQR 25-75). SAH: Subarachnoid hemorrhage, IPH: Intraparenchymal hemorrhage, HDL-C: High density lipoprotein cholesterol, LDL-C: Low density lipoprotein cholesterol, NLR: Neutrophil to lymphocyte ratio, MLR: Monocyte to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, AIP: Atherogenic index of plasma.

**Table 3.** Comparison of laboratory parameters between treatment methods in patients with intraparenchymal hemorrhages (*n* = 154)

| | Conservative Treatment (*n* = 139) | Surgical Treatment (*n* = 15) | *P* |
|---|---|---|---|
| NLR | 3.5 (1.9-7.9) | 3.9 (1.9-7.7) | *0.910* |
| MLR | 0.33 (0.3-0.5) | 105.6 (67.3-332.9) | *0.573* |
| PLR | 130.9 (93.1-200) | 0.32 (0.2-0.6) | *0.796* |
| AIP | 0.51 (0.3-0.6) | 0.47 (0.04-0.7) | *0.776* |

Values are expressed as median (IQR 25-75). NLR: Neutrophil to lymphocyte ratio, MLR: Monocyte to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, AIP: Atherogenic index of plasma.

in 48 hours, 70 (39.8%) at 1 month, and 75 (42.6%) at 3 months.

**Table 2** compares the laboratory parameters in patients with ICH. Patients with IPH exhibited significantly elevated NLR, MLR, PLR, and AIP values compared to those with SAH ($P < 0.05$). Among the lipid profile, only HDL levels were significantly decreased in IPH patients compared to those with SAH ($P < 0.001$).

**Table 3** presents a comparison of laboratory parameters in IPH patients. No substantial differences in NLR, MLR, PLR, or AIP were observed between patients receiving conservative versus surgical treatment ($P > 0.05$).

**Table 4** compares admission laboratory parameters between surviving and deceased subgroups in patients with ICH. The NLR, MLR, PLR, and AIP were not significantly different among patients who died within 48 hours, at 1 month, or 3 months ($P > 0.05$). Due to the lack of significance, we were unable to perform the regression model for prognosis prediction.

## Discussion

To the best of our knowledge, this is the first study to assess the prognostic value of multiple inflammatory ratios in patients with ICH. In our study of 176 patients, we found that the NLR, MLR, PLR, and AIP values were significantly elevated in the IPH group compared to the SAH group. However, these indices were not associated with prognosis in patients with ICH.

The diagnostic and predictive values of these ratios have recently received increasing attention in patients with ischemic stroke [8, 20]. Increasing evidence suggests that immune-derived inflammatory mechanisms are critical in the pathogenesis of ischemic stroke [21-23]. Neutrophils are the first cells to migrate to the ischemic area, where they secrete inflammatory cytokines including tumor necrosis factor-α, interleukin-6, and adipokines, leading to an enhanced immune response [22, 23]. Lymphocytes are thought to promote neurofunctional improvement [21, 23], whereas monocytes and neutrophils are presumed to exacerbate brain damage [23]. Accumulation of platelets in the damaged area leads to thrombosis, which is detrimental to recovery [21]. Therefore, the NLR, MLR, and PLR - readily available markers - may indicate the immune-derived inflammatory response. Previous studies have shown that the NLR, MLR, and PLR are predictive of

**Table 4.** Comparison of admission laboratory parameters between survivor and exitus groups within 48 hours, 1-month, and 3-month in patients with intracerebral hemorrhage (*n* = 176)

| | Within 48 hours (*n* = 30) | | | 1-month (*n* = 70) | | | 3-month (*n* = 75) | | |
|---|---|---|---|---|---|---|---|---|---|
| | *Survivor (n = 146)* | *Exitus (n = 30)* | *P* | *Survivor (n = 106)* | *Exitus (n = 70)* | *P* | *Survivor (n = 101)* | *Exitus (n = 75)* | *P* |
| NLR | 3.2 (1.9-7.1) | 6.5 (1.3-10.9) | *0.338* | 2.7 (1.9-6.6) | 4.8 (1.7-10.7) | *0.120* | 2.7 (1.9-6.7) | 4.4 (1.7-10.1) | *0.212* |
| MLR | 0.3 (0.2-0.5) | 0.4 (0.2-0.6) | *0.300* | 0.3 (0.2-0.5) | 0.4 (0.2-0.6) | *0.135* | 0.3 (0.2-0.5) | 0.3 (0.2-0.6) | *0.240* |
| PLR | 121 (87.6-196.6) | 128.2 (64.5-230) | *0.815* | 124.1 (89-199.2) | 117.9 (73.6-194.7) | *0.288* | 135.2 (89-200) | 117.5 (73.6-191.7) | *0.130* |
| AIP | 0.4 (0.2-0.6) | 0.4 (0.1-0.6) | *0.786* | 0.4 (0.2-0.6) | 0.4 (0.2-0.6) | *0.760* | 0.4 (0.2-0.6) | 0.3 (0.1-0.6) | *0.436* |

Values are expressed as median (IQR 25-75). NLR: Neutrophil to lymphocyte ratio, MLR: Monocyte to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, AIP: Atherogenic index of plasma.

clinical outcomes in ischemic stroke patients [21-23].

However, data on hemorrhagic stroke are limited. The majority of ICH cases are due to chronic hypertension, which is closely related to arterial stiffness resulting from increased inflammation in the arterial wall. Therefore, we hypothesized that inflammatory ratios are also involved in ICH. The NLR has become recognized as a biomarker of inflammation among these. Two reports have demonstrated a link between a high value of admission NLR and unfavorable prognosis in patients with ICH [9, 10]. Babu et al. studied 158 patients with ICH and found that high NLR was a strong indicator of functional outcome at 90 days [11]. Mishra et al. demonstrated that an elevated NLR (> 7) was associated with poorer outcomes, including increased mortality and morbidity, three months following ICH [12]. A recent study by Wang et al. showed that the NLR is an independent factor influencing delayed cerebral ischemia after ICH [24]. In contrast, we lacked an association between NLR and mortality during the 3-month period following ICH. This lack of difference may be explained by the short follow-up period - long-term results could be different. Additionally, the release of monocytes from the bone marrow into circulation is induced particularly under inflammatory conditions, and monocytes migrate to sites of infection where they mature into macrophages [13]. A retrospective study by Jiang et al. [13] evaluated the MLR in 771 patients with acute hemorrhagic stroke based on cranial computed tomography images. The findings indicated that the admission MLR was linked to a high risk of in-hospital mortality, with an odds ratio of 3.13 (95% confidence interval). The area under the curve for the MLR in predicting in-hospital mortality was calculated to be 0.62, with an optimal cut-off value of 0.71 [13]. Contrarily, we did not obtain an association between MLR and mortality during the 3-month period following ICH. This may be due to the frequent use of oral nonsteroidal anti-inflammatory drugs, particularly in older adults, to relieve musculoskeletal and joint pain. Furthermore, no data have been reported concerning the role of PLR in patients with ICH. Previous works have shown that an elevated PLR is associated with a higher risk of hemorrhagic transformation [5, 15] and increased in-hospital mortality [6] in ischemic stroke patients. In the present study, PLR values were not significantly different between surviving and deceased subgroups in patients with ICH. This may be linked to the small sample size. Moreover, the AIP is currently considered a surrogate marker for small LDL particle size and has emerged as a novel indicator of dyslipidemia [16]. Prospective reports have shown that elevated AIP levels are linked to unfavorable outcomes in cases with ischemic stroke [25, 26]. Our study is the first to examine AIP in patients with ICH. The AIP values were not associated with short-term mortality in ICH patients, possibly owing to the small size. On the other hand, we found that the NLR, MLR, PLR and AIP at admission were significantly elevated in the IPH group compared to the SAH group. This may indicate the involvement of vascular neuroinflammatory mechanisms in the pathogenesis of IPH, similar to those observed in ischemic injury. A previous study showing the relation of high AIP levels with increased arterial stiffness and hypertension [17], may support this hypothesis. Larger cohorts are needed to draw definitive conclusions.

The primary limitations of this study include the limited number of patients in the SAH group and the small size representing a single

institute, which restrict the broader applicability of our results. Potential confounding factors that could influence inflammatory status, such as medications for blood pressure control and secondary infections, were not analyzed and may have affected our results. Additionally, the study was retrospective and lacked a control group. The inflammatory ratios at admission may have changed during hospitalization, and repeated measurements might have yielded different results.

## Conclusions

This study is the first to assess composite inflammatory ratios in patients with ICH. Our findings revealed that the NLR, MLR, PLR, and AIP at admission were significantly elevated IPH patients than in those with SAH, suggesting the involvement of vascular neuroinflammatory mechanisms in the pathogenesis of IPH. However, our findings do not support the use of these markers for short-term risk prediction. Larger cohorts with longitudinal follow-up are needed.

## Disclosure of conflict of interest

None.

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