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Evaluation of the performance of pan-immune inflammation value in predicting in-hospital mortality in patients with spontaneous intracerebral hemorrhage

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Abstract

Background & Objective: Spontaneous intracerebral hemorrhage (ICH) is associated with high mortality and poor functional prognosis. This study aimed to evaluate the prognostic significance of the pan-immune inflammation value (PIV) at admission in predicting in-hospital mortality in patients with spontaneous ICH. Additionally, we compared the predictive performance of PIV with other inflammatory indices such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII). *Methods:* This retrospective study included 102 consecutive patients admitted within 24 hours of the onset of spontaneous ICH. Patients were categorized into two groups: survivors at discharge and those who died in the hospital. The groups were compared based on NLR, PLR, SII index, and PIV. Logistic regression and ROC analyses were performed to evaluate the predictive performance of PIV compared to NLR, PLR, and SII index for in-hospital mortality. *Results:* Patients who died in the hospital (n=45) had a higher mean age, higher NIHSS score, larger hematoma volumes, and a higher incidence of diabetes, intraventricular extension, and surgical intervention. Additionally, these patients had higher PIV, NLR, PLR, and SII index values ($p<0.05$). PIV demonstrated superior performance compared to these three markers in predicting in-hospital mortality.
Conclusion: The results of our study suggest that PIV may serve as a valuable prognostic indicator for predicting in-hospital mortality in patients with spontaneous ICH. This study is the first to evaluate PIV as a potential predictive marker for mortality in ICH patients.

Keywords: Stroke, intracerebral hemorrhage, pan-immune inflammation value

INTRODUCTION

Stroke is the second most common cause of death worldwide. Ischemic strokes comprise 87% of all strokes, 10% are caused by intracerebral hemorrhages (ICH), and 3% by subarachnoid hemorrhages.[1] Of intracranial hemorrhages, 85% present as spontaneous ICH. Intracerebral hemorrhage is a stroke subtype with a high mortality rate, with a 5-year survival rate of 29%. Only 12% of discharged patients are functionally independent, with severe neurological deficits commonly persist as long-term consequences.[2]

Recently, preclinical and clinical studies indicated that inflammatory processes in brain injury after ICH could affect ICH prognosis spontaneous intracerebral hemorrhage.[3,4] Inflammation is one of the most important defense mechanisms against brain damage following hemorrhage. Blood products that leak from damaged vessels bind to receptors on the surface of microglia, initiating a pro-inflammatory response. The influx of neutrophils and monocytes further enhances the production of reactive oxygen species (ROS) and the release of pro-inflammatory substances such as TNF-α and IL-1β.[2,5-7]

The neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII) are useful, cost-effective, and commonly used indicators of peripheral systemic inflammation.[8-10] Several studies have shown that NLR and PLR are

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prognostic indicators for hematoma expansion in ICH, early worsening after stroke, and mortality.[11-14] The SII, a novel, cost-effective inflammation marker indicates simultaneous immune and inflammatory status; it is a more accurate indicator of overall inflammatory status, compared with NLR and PLR (15). Furthermore, the SII can predict severity and prognosis in conditions such as stroke, cardiovascular diseases, atherosclerotic diseases, and cancers.[15-20]

The pan-immune inflammation value (PIV) is a newly defined comprehensive index that accounts for all blood cell groups related to systemic inflammation and immunity.[21,22] It has proven to be a strong predictor in determining poor prognosis in patients with acute ischemic stroke, predicting hemorrhagic transformation, and outcomes in patients receiving thrombolytic therapy. There are no studies in the literature related to ICH.[23]

In this study, we aimed to evaluate the relationship between the PIV and in-hospital mortality in patients with spontaneous ICH, and to compare its predictive value for mortality with the NLR, PLR, and SII markers.

METHOD

This study was conducted with patients who had a confirmed diagnosis of spontaneous ICH among the consecutive patients admitted to the Neurology Intensive Care Unit or Neurology inpatient service between January 2011 and December 2021. The study was designed as a single-center, retrospective, cross-sectional study and was approved by the Clinical Research Ethics Committee of Inonu University Faculty of Medicine with 2023/4430 protocol number. The study was performed in accordance with the Declaration of Helsinki.

For the study, the primary criteria for patient selection was the confirmed diagnosis of spontaneous ICH based on medical history, neurological examination, and neuroradiological assessments. Inclusion criteria for the study were supratentorial location of ICH, patients within the first 24 hours of clinical symptom, experiencing ICH for the first time, patients in whom ICH was detected by at least one neuroimaging method (non-contrast brain CT or MRI) at the time of hospital admission, patients with complete peripheral blood laboratory data within the first 24 hours of hospital admission, patients who died in the hospital.

Exclusion criteria for the study were patients with a history of transient ischemic attack, ischemic stroke, or cerebral venous thrombosis, patients with intracerebral hemorrhage secondary to any other cause (primary epidural, subarachnoid, subdural, or intraventricular hemorrhage, vascular malformations, aneurysm, tumor, trauma, etc.), patients with a history of infection within the 2 weeks prior to ICH, patients with severe liver and kidney conditions, leukemia, lymphoma, other hematological diseases, or malignant tumors, presence of active infection (e.g., pneumonia, urinary tract infection, COVID-19) detected at the time of admission and using anticoagulants.

Using our hospital's routinely utilized database, information was obtained on patients' demographic data (age, gender), vascular risk factors, NIHSS (National Institutes of Health Stroke Scale) score at admission, radiological findings (hemorrhage location, volume, and ventricular extension), laboratory tests (biochemistry, complete blood count), length of hospital stay, neurosurgical interventions performed (e.g., decompressive craniectomy, extraventricular drainage (EVD) placement). The patients' vascular risk factors (hipertension, diabetes mellitus) and history of smoking and alcohol use were recorded.

The volume of the hematoma on brain CT was calculated using the formula AxBxC/2. In this formula, A represents the maximum diameter of the hematoma on the axial slice, B is the diameter perpendicular to A, and C denotes the number of slices in which the hematoma is visible.[24]

The location of the hemorrhage was classified as lobar, deep supratentorial, and infratentorial.

The NLR was calculated using the formula neutrophil/lymphocyte , PLR using the formula platelet/lymphocyte, and SII using the formula neutrophil × platelet / lymphocyte and PID was calculated using the formula: neutrophil count × platelet count × monocyte count / lymphocyte count ratio.

Patients who met the study criteria were divided into two groups: survivors and those who died during hospitalization.

Statistical analysis

Statistical analyses were performed using SPSS for Windows version 25.0 (IBM Corp., Armonk, NY, USA). The normality of continuous variables was verified using the Shapiro–Wilk test ($n < 50$) and Kolmogorov–Smirnov test ($n \geq 50$). Differences between survivor and non-survivor patients were assessed using the Mann–Whitney U test for independent non-normally distributed variables and independent t-tests for normally

distributed variables. Binary logistic regression analysis was used to assess the efficacy of NLR, PLR, SII index, and PIV in predicting clinical outcomes. ROC (Receiver Operating Characteristic) curve analysis was performed to define the cut-off values PIV for predicting in-hospital mortality in patients with ICH. A p-value of <0.05 was considered statistically significant in all analysis.

RESULTS

A total of 102 patients were included in the study, comprising 56 males (54.9%) and 46 females (45.1%). Among these patients, 57 (55.9%) survived, while 45 (44.1%) died in the hospital. The demographic information of the patients included in the study is shown in Table 1.

No significant differences were found between survivor and non-survivor groups in the analysis of variables such as hypertension, smoking, alcohol consumption, length of hospital stay, mean systolic and diastolic blood pressure, location of hemorrhage, or complete blood count parameters including hemoglobin, hematocrit, and lymphocytes. Significant differences were found between the survivor and non-survivor groups in terms of age, diabetes mellitus (DM), hematoma volume, intraventricular spread, rate of surgical treatment, rate of external ventricular drain (EVD) placement, and complete blood count parameters such as leukocyte, neutrophil, monocyte, and platelet counts, which were higher in the non-survivor group (Table 2). Peripheral inflammation markers, including NLR, PLR, SII, and PIV, were also significantly higher in the non-survivor group compared to the survivor group (Table 2).

ROC curve analysis and the Youden index were utilized to determine the optimal PIV cutoff for distinguishing between survival and mortality status in patients with intracerebral hemorrhage, demonstrating an area under the ROC curve of 77.3 (95% confidence interval [CI], 0.683–0.862; Figure 1) and an optimal cutoff value of 157.71, with sensitivity and specificity values of 93% and 97.8%, respectively (Table 3).

In the logistic regression analysis, NLR, PLR, SII, and PIV did not demonstrate any statistically significant predictive value for mortality in patients with intracerebral hemorrhage (Table 4).

When comparing the PIV marker with other variables, it was found to have the highest sensitivity (0.978) and the highest specificity (1-0.930). It was also determined to be a more effective marker than the other three markers (NLR, PLR, SII index) in predicting survival and in-hospital mortality in patients with intracerebral hemorrhage (Table 3).

DISCUSSION

ICH is a type of stroke characterized by a high risk of mortality or permanent disability, representing a life-threatening condition.[25] Inflammation plays a crucial pathophysiological role in hemorrhagic stroke, similar to its role in other systemic diseases. Both central and peripheral immune cells are involved in the inflammatory process surrounding the hematoma.[26,27] Following intracerebral hemorrhage, secondary chronic damage caused by oxidative stress, cell death, and a robust inflammatory response in the perihematomal tissue can persist for days to months, tracing the primary brain injury caused by mechanical effects of the hematoma.[27-29] Previous studies have demonstrated that peripheral inflammation is associated with hematoma enlargement, increased systemic complications, and poor prognosis in ischemic stroke.

In patients with ICH, analysis of the tissues surrounding the hematoma revealed neutrophil infiltration within 8 hours, which increased further by 1 day.[30] Neutrophils contribute to neurotoxicity by releasing pro-inflammatory cytokines such as TNF-α and IL-1β, which in turn increase capillary permeability, disrupt the blood-brain barrier, and exacerbate brain edema.[31] During the acute phase following ICH, there is

Table 1: Demographic and clinical characteristics of patients

All patients (n=102)	Mean±SD (Min-Max)
Sex (male/female)(n,%)	56(54.9) /46(45.1)
Age (years)	71.49 ± 14.05 (22-102)
Initial Systolic Blood Pressure (mmHg)	177.53 ± 41.42 (54-259)
Initial Diastolic Blood Pressure (mmHg)	96.29 ± 20.89 (40-140)
National Institutes of Health Stroke Scale (NIHSS)	12.34 ± 8.75 (1-27)
Duration of hospital (day)	16.09 ± 14.37 (2-85)

Table 2: Baseline characteristics of patients

	Survivor group (n=57)	Non-survivor group (n=45)	
	mean±SD(min-max)	**mean±SD(min-max)**	**p value**
Demographics			
Age	66.84 ± 14.01((22-101)	77.38 ± 11.83(52-102)	0.001*
Sex (Female/male)(n,%)	22(47,8)/35(62,5)	24(52,2)/21(37,5)	0.137
National Institutes of Health Stroke Scale (NIHSS)	6.11 ± 4.71(1-21)	20.24 ± 5.76(5-27)	0.001*
Initial Systolic Blood Pressure (mmHg)	173.25 ± 35.07(110-231)	182.96 ± 48.16(54-259)	0.242
Initial Diastolic Blood Pressure (mmHg)	93.74 ± 17.68(57-130)	99.53 ± 24.19(40-140)	0.165
Duration of stay	16.72 ± 11.5 (4-60)	15.29 ± 17.45(2-85)	0.620
Vasculer risk factors			
Hypertension (n,%)	33(50)	33(50)	0.105
Diabetes mellitus (n,%)	6(33.3)	12(66.7)	0.034*
Smoking(n,%)	7(46.7)	8(53.3)	0.511
Alchol use (n,%)	2(40)	3(60)	0.572
Intracerebral hemorrhage parameters			
Volume	23.01 ± 30.39(0.5-175)	91.82 ± 48.28 (20-180)	0.001*
Intraventricular extension(n,%)	20(37)	34(63)	0.001*
Supratentorial location(n,%)	38(53.5)	33(46.5)	0.733
Infratentorial location(n,%)	9(64.3)	5(35.7)	
Lobar location(n,%)	10(58.8)	7(41.2)	
Decompresif surgery(n,%)	6(54,5)	23(76,7)	0.002*
Extraventriculer drainage(n,%)	1(5.3)	18(94.7)	
Laboratory data			
Absolute lymphocyte Count	1.54 ± 0.78 (0.4-4.82)	1.39 ± 0.57(0.2-3.2)	0.281
Absolute neutrophil count	7.62 ± 4.04(1.77-21)	12.69 ± 5.17 (2.71-22)	0.001*
Absolute monocyte count	0.57 ± 0.3(0.17-1.65)	0.94 ± 0.85(0.23-3.5)	0.003
Leukocyte	10.32 ± 3.88 (4.15-21.9)	14.6 ± 5.27 (5.3-24.2)	0.001*
Platelets	237.21 ± 466(140-332)	284.51 ± 87.55(104-615)	0.001*
Hemoglobin	14.45 ± 1.9(10.1-20.5)	14.34 ± 2.27(7.8-19.1)	0.799
Hematocrit	43.04 ± 5.34(31.6-62.9)	43.49 ± 5.75 (27.3-56.7)	0.682
Neutrophil-to-lymphocyte ratio (NLR)	6.95 ± 6.54 (0.93-35)	12.35 ± 15.18(1.33-104.5)	0.017*
Platelet-to-lymphocyte ratio (PLR)	193.48±109.34(49.17-582.5)	274.18 ± 278.18(81.56-1745)	0.048*
Systemic immune-inflammation index (SII)	1706.21 ± 1716.58(220.59-7980)	3670.81 ± 5360.15(299.03-36470.5)	0.011*
Pan-immune inflammation value (PIV)	968.31 ± 1175.78 (66.18-5963,71)	4036.12 ± 7635.3(155.5-47411.65)	0.003*

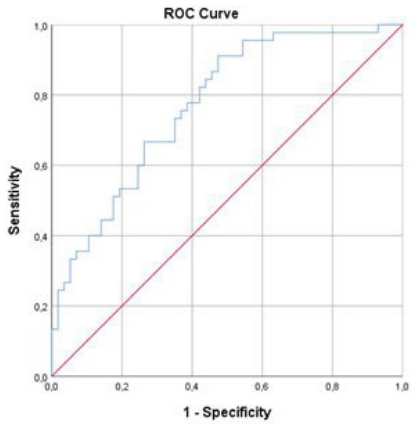

Figure 1: ROC curve analysis of PIV for intracerebral hemorrhage patients

an overactivation of the sympathetic nervous system and the hypothalamic–pituitary–adrenal axis, leading to increased levels of catecholamines and steroids. This overactivation contributes to systemic immunosuppression and further induces functional inactivation and apoptosis of peripheral lymphocytes.[32] Reduced lymphocyte counts impair immune function, elevate the risk of post-ICH infections, and may affect functional outcomes.[33,34]

Platelets are an integral component of the hemostatic system.[35] The balance of platelet aggregation is broken after ICH. The increase of platelet counts in the peripheral circulation induces a hypercoagulable state, which increases the risk

Table 3: ROC curve analysis of neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, systemic immune-inflammation index and pan-immune inflammation value cutoff values for predicting mortality status

Variables	Cut-off	Specificity	Sensitivity	AUC	p-value	95% CI	
						Lower bound	Upper bound
Neutrophil-to-lymphocyte ratio (NLR)	2.84	0.956	0.667	0.715	0.001*	0.616	0.815
Platelet-to-lymphocyte ratio (PLR)	98.05	0.933	0.860	0.601	0.001*	0.491	0.711
Systemic immune-inflammation index (SII)	301.95	0.978	0.895	0.742	0.001*	0.645	0.838
Pan-immune inflammation value (PIV)	157.71	0.978	0.930	0.773	0.001*	0.683	0.862

Table 4: Predictive values of neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, systemic immune-inflammation index and pan-immune inflammation value for mortality status

Variables	β	S.E.	W	sd	Sig. (p)	Exp(β) (OR)	95% CI Exp(β)	
							Lower bound	Upper bound
Pan-immune inflammation value	0.000	0.000	2.843	1	0.092	1.000	1.000	1.001
Neutrophil-to-lymphocyte ratio	-0.127	0.095	1.780	1	0.182	0.881	0.731	1.061
Platelet-to-lymphocyte ratio	-0.003	0.003	0.519	1	0.471	0.997	0.991	1.004
Systemic immune-inflammation index	0.001	0.000	1.804	1	0.179	1.001	1.000	1.002
Constant	-0.754	0.481	2.451	1	0.117	0.471		

of poor outcomes.[33] Activated platelets release a series of potent chemical mediators (i.e.,adenosine diphosphate, serotonin, thromboxane A2, and TGFβ), all of which may potentially play important roles in brain damage and unfavorable prognosis.[35]

Numerous studies in the literature have reported that peripheral inflammatory markers obtained from a complete blood count, including various cell types such as NLR, TLR, and SII, are useful in monitoring and/or predicting the prognosis of many diseases, besides evaluating individual blood cells.[7-12]

NLR is a repeatable, easily accessible marker that reflects the balance between neutrophil count, which indicates the innate immune response, and lymphocyte count, which represents the adaptive immune response in the inflammatory reaction to injury.[36,37] It is an indicator of chronic inflammation and provides information about the level of inflammation.[36-38] Studies in the literature have reported a significant relationship between NLR levels and the severity of stroke (ischemic or hemorrhagic) in patients. Additionally, NLR has been identified as a marker that can be used to predict early neurological deterioration after stroke, hemorrhage expansion in ischemic stroke, as well as short-term prognosis and in-hospital mortality in patients with acute ischemic stroke undergoing intravenous thrombolytic therapy or endovascular treatment.[38,39]

Similarly, it has been shown that high levels of PLR and SII are associated with severe stroke and poor functional prognosis in patients with acute ischemic stroke.[40,41] Additionally, in spontaneous ischemic stroke patients, these markers are linked to hematoma expansion, early neurological deterioration, poor prognosis in patients undergoing surgical treatment due to spontaneous ischemic stroke, and early neurological impairment in patients receiving thrombolytic therapy or mechanical thrombectomy for acute ischemic stroke.[40-43]

PIV, a novel indicator of inflammation, is calculated using values from four different inflammatory cells: neutrophils, platelets, monocytes, and lymphocytes, making it more comprehensive than the other three indices. As such, it serves as a good index for reflecting both local immune responses and systemic inflammation in humans. Few studies have demonstrated that PIV is a strong index for predicting poor prognosis in patients with acute ischemic stroke, hemorrhagic transformation, and in those receiving thrombolytic therapy.[23]

In the literature, no studies have been found that asses the association between PIV and prognosis in patients with spontaneous ischemic stroke. In our study, we found that PIV was significantly higher in patients who died from ischemic stroke compared to survivors, and it is a significant marker for predicting in-hospital mortality in these patients. Our results suggest that PIV is a more effective parameter than other markers (NLR, PLR, and SII index) in predicting mortality in patients with intracerebral hemorrhage. The ROC analysis indicated that a cutoff value of 157.71 for PIV has the highest sensitivity and specificity as a test for predicting in-hospital mortality.

Our study has several limitations. These include its retrospective and single-center design, as well as the relatively small number of patients included in the study.

In conclusion, PIV, which is calculated using a larger number of peripheral blood cells compared to previously studied markers such as NLR, PLR, and the SII index, has been found to be more effective in predicting in-hospital mortality in patients with spontaneous intracerebral hemorrhage. This study is the first in the literature on this topic and is notable for evaluating whether PIV has an advantage over traditional markers.

DISCLOSURE

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Conflict of Interest: None

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