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Original article

ICAM-1 and platelet counts as biomarkers for severity and outcomes in acute ischemic stroke: a cross-sectional study

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Abstract. *Background and aim:* Stroke is a major global cause of death and disability. Timely intervention is essential to reducing both mortality and disability in ischemic stroke patients. Biomarkers such as Intercellular Adhesion Molecule-1 (ICAM-1), which is involved in inflammation and tissue damage, and platelet count (PC), which reflects platelet activity, are hypothesized to aid in predicting stroke outcomes. The objective of this study was to evaluate the relationship between serum ICAM-1 levels, platelet count, stroke severity, and clinical outcomes in patients with acute ischemic stroke. *Methods:* A cross-sectional study was conducted in 63 patients with ischemic stroke. Serum ICAM-1 levels were measured via ELISA, platelet count through standard blood tests, and stroke severity using the National Institutes of Health Stroke Scale (NIHSS). Clinical outcomes were assessed with the modified Rankin Scale (mRS). *Results:* The study found that stroke patients had higher mean levels of ICAM-1 compared to control participants, but the difference was not statistically significant (p = 0.888) and the mean platelet count in stroke patients was lower than in control participants, but the difference was also not significant (p = 0.13). Additionally, there was no significant association or correlation between ICAM-1 levels and NIHSS scores or mRS scores, as well as between platelet count levels and NIHSS scores or mRS scores. *Conclusions:* Based on the results of this study, ICAM-1 levels and platelet counts may not serve as reliable biomarkers for assessing the severity of acute ischemic stroke or predicting clinical outcomes. (www.actabiomedica.it)

Key words: acute ischemic stroke, ICAM-1, platelet counts, stroke biomarkers, stroke severity, clinical outcomes in stroke

Background

Acute stroke refers to the sudden appearance of localized neurological impairments in a specific vascular region of the brain, retina, or spinal cord, caused by underlying cerebrovascular conditions (1,2). Globally, 68% of all strokes are caused by ischemia, and 32% are caused by hemorrhage (3). Additional data from a multicenter study involving 5,411 hospitalized stroke patients showed that strokes caused by subarachnoid hemorrhage accounted for 3.3%, intracerebral hemorrhage for 29.6%, and ischemic stroke for 67.1% (4). According to the World Health Organization (WHO) (2021), stroke is the second leading cause of death and the leading cause of disability globally. In Indonesia, compared to other Southeast Asian countries, it has the highest mortality rate based on age and gender (193.3/100,000) and the highest age-adjusted disability rate (3,382.2/100,000) (4,5). One of the markers that can predict the severity and clinical outcomes of ischemic stroke patients is Intercellular Adhesion Molecule-1 (ICAM-1). ICAM-1, also known as

CD54, is a cell surface glycoprotein that is overexpressed on endothelial cells and epithelial cells in response to various inflammatory mediators and immune system activation (6). Increased levels of systemic inflammatory markers in the blood are associated with poor outcomes following acute ischemic stroke. A study in Finland showed that ICAM-1 expression significantly increased after acute ischemic stroke, suggesting a potential mechanism by which ICAM-1 worsens neurological damage in stroke. In contrast to the above study, a clinical study in Croatia found no correlation between serum ICAM-1 levels and stroke severity (7). Another mechanism suspected to play a role in the severity and clinical outcomes of stroke is thromboinflammation. Thromboinflammation is a complex process involving the interaction between thrombosis, mediated by platelets, and inflammation, mediated by the immune system, with the end result being brain injury and an increased severity of the stroke. A study by Yang et al. concluded that in ischemic stroke patients with a normal platelet count, platelet count (PC) could be a good predictor for long-term recurrent stroke, mortality, and poor clinical outcomes (8). A reliable tool for assessing the initial severity of a stroke and predicting mortality in acute ischemic stroke patients is the National Institutes of Health Stroke Scale (NIHSS). This prediction of mortality aids in determining the clinical severity. To evaluate clinical prognosis, the Modified Rankin Scale (mRS) is used, which provides a more effective assessment of functional recovery following a stroke (9). Further investigation is needed to elucidate the relationship between serum ICAM-1 levels and platelet parameters, particularly Platelet Count (PC), in the context of acute ischemic stroke severity and outcomes. Such research could enhance our understanding of the complex interplay between inflammation, thrombosis, and clinical prognosis.

Methods

This cross-sectional study was conducted at Dr. Wahidin Sudirohusodo Hospital Makassar in 2024 with 63 participants who met the inclusion criteria. The inclusion criteria for this study were the population whose first stroke symptoms appeared suddenly (onset less than 7 days) aged 18 years to 80 years in the South Sulawesi region who were admitted through the Emergency Room at our institution. Patients with chronic kidney disease, chronic heart failure, malignancy, systemic infections, severe liver disease, or autoimmune disorders were excluded. The control group consisted of subjects with demographic similarities to the case group who met the inclusion and exclusion criteria.

Determination of stroke patients

Stroke was diagnosed based on anamnesis, revealing a sudden onset of focal neurological deficits, such as motor impairments like extremity weakness or sensory disturbances, identified during a neurological examination. This was further confirmed by a non-contrast head CT scan performed using a Siemens Somatom Go Top 128 Slice (Erlangen, Germany), which displayed a hypodense area indicative of ischemic damage within the brain tissue.

Variables and degree of severity

Participants data included age, gender, comorbidities (hypertension, diabetes mellitus, and smoking), ICAM-1, Platelet Count, NIHSS and mRS. Severity of stroke is assessed using NIHSS, with scores categorized into minor (0–4), moderate (5–15), moderate-to-severe (16–20), and severe (21–42). While, mRS scores categorized into favourable (0–2) and unfavourable (3–6).

National institute of health stroke scale

The National Institute of Health Stroke Scale (NIHSS) is the gold standard for assessing stroke severity. At admission, motor, sensory, and cognitive function change scores comprise 11 assessment components. In this study, it is used to indicate the degree of severity (10).

The modified rankin scale

Widely validated and highly reliable, the mRS is commonly used to assess stroke patients. Its efficient application for initial evaluation and ongoing monitoring enables healthcare providers to make well-informed decisions regarding timely referrals to specialized care and the initiation of appropriate early interventions (11).

ICAM-1 level

Human ICAM-1 levels are quantified using an ELISA kit (Elabscience, USA from Genetika Science Indonesia, catalog number E-EL-H6114).

Statistical analysis

Data analysis will use various statistical techniques. The normality of the data is evaluated with the Shapiro-Wilk test for samples smaller than 50 and the Kolmogorov-Smirnov test for larger samples. To compare ICAM-1 levels and platelet count with NIHSS scores and mRS score from the patients, one-way ANOVA is applied for normally distributed data, and Kruskal-Wallis ANOVA is used for non-normally distributed data. The relationship between soluble ICAM-1 levels and NIHSS scores is examined using Pearson's correlation test (for parametric data) or Spearman's test (for non-parametric data). Additionally, the correlation between platelet count (PC) and NIHSS scores, as well as the association between PC and clinical outcomes, is assessed using appropriate correlation methods. All statistical tests are performed using SPSS ver 27, with a significance threshold of $p < 0.05$.

Results

Characteristics of participants

Among the 63 patients with ischemic stroke included in the study, and 22 patients as control group. Table 1 shows the results of the characteristics of the study participants.

Table 1. Characteristics of study participants.

Variables		Ischemic Stroke	%	Control (n=22)	%
Gender	Male	34	54%	11	50%
	Female	29	46%	11	50%
Age (Year)	25-43	3	5%	1	4.5%
	44-59	34	54%	11	50%
	60-74	24	38%	10	45.5%
	> 75	2	3%	0	0%
Hypertension	Yes	38	60.3%	8	36.4%
	No	25	39.7%	14	63.6%
DM	Yes	11	17.5%	4	18.2%
	No	52	82.5%	18	81.8%
Smoking Status	Yes	17	27%	6	27.3%
	No	46	73%	16	72.7%
Score NIHSS on admission	Mild (0-4)	27	42.9%	0	0%
	Moderate (5-15)	32	50.8%	0	0%
	Moderate-Severe (16-20)	3	4.8%	0	0%
	Severe (21-42)	1	1.6%	0	0%
mRS Onset day 30	Favourable (0-2)	37	58.7%	0	0%
	Unfavourable (3-6)	26	41.3%	0	0%
Total		63	100%	22	100%

Abbreviations: DM, Diabetes Mellitus; NIHSS, National Institute of Health Stroke Scale; mRS, The Modified Rankin Scale.

As shown in Table 1, the demographic data of stroke patients from all subjects show that males (34 subjects, 54%) have a higher proportion compared to females (29 subjects, 46%). In contrast, the control group consists of 11 male subjects (50%) and 11 female subjects (50%). Univariate analysis revealed that the severity of stroke ischemic at admission, based on NIHSS scores from days 1 to 7 (admission), revealed that 27 subjects were categorized as mild, 32 subjects as moderate, 3 subjects as moderate-to-severe, and 1 subject as severe. Clinical outcomes, measured using mRS scores on day 30 after onset, showed favourable in 37 subjects and unfavourable in 26 subjects. The mean ICAM-1 level was higher in acute ischemic stroke patients (18.257 ng/mL) than in controls (16.703 ng/mL), but the difference was not significant (p = 0.888). Similarly, platelet counts were higher in the control group, but the difference was also not significant (p = 0.13) (Table 2).

The study revealed no significant differences in ICAM-1 levels or platelet counts between acute ischemic stroke patients and the control group, with mean ICAM-1 levels of 18.257 ng/mL and 16.703 ng/mL, respectively (p = 0.888), and platelet counts being higher in the control group (p = 0.13). ICAM-1 levels showed no significant association with stroke severity based on NIHSS scores at admission (Kruskal-Wallis test, p = 0.393) or with clinical outcomes measured by the mRS score (Mann-Whitney test, p = 0.635; Spearman's correlation, r = -0.060, p = 0.639). Similarly, platelet counts demonstrated no significant differences across NIHSS severity categories (Mann-Whitney test, p = 0.484) or correlation with stroke severity (Spearman's correlation, r = 0.050, p = 0.699). Platelet counts also showed no significant differences between mRS outcome groups at day 30 (Mann-Whitney test, p = 0.610) or correlation with mRS outcomes (Spearman's correlation, r = 0.065, p = 0.614). Overall, ICAM-1 levels and platelet counts were not significantly associated with stroke severity or clinical outcomes (Table 3 and Table 4).

Table 2. Comparison of ICAM-1 and Platelet Count in Ischemic Stroke Patients and Control Group.

Variables	Mean (*Minimum-Maximum*)		*p*-value
	Ischemic Stroke	Control	
ICAM-1	18.257 (6.480-56.901)	16.703 (6.186-25.873)	0.888*
Platelet Count	252.73 (44-576)	271.82 (218-321)	0.13*

**Mann Whitney Test*

Table 3. Comparison of mean ICAM-1 levels and platelet counts based on NIHSS and mRS.

Stroke Severity		ICAM-1 Mean (*Min-Max*)	*p*-value	*Platelet Count* Mean (*Min-Max*)	*p*-value
NIHSS on admission	Mild	17.896 (6.480-47.931)	0.393	241.44 (44-313)	0.484**
	Moderate	18.981 (10.736-56.901)		260.44 (102-576)	
	Moderate-Severe	13.137 (9.498-19.460)		239 (162-291)	
	Severe	20.178		352	
Clinical Outcome					
mRS Onset day 30	Favourable	17.876 (8.309-34.018)	0.635	243.00 (44-342)	0.610*
	Unfavourable	18.799 (6,480-56,901)		266.58 (79-576)	

***Kruskal-Wallis test, *Mann Whitney Test*

Table 4. Relationship between ICAM-1 levels and platelet counts based on NIHSS and mRS score.

Stroke Severity	ICAM-1		Platelet Count	
	r-value	*p*-value	*r*-value	*p*-value
NIHSS on admission	0.038	0.765	0.050	0.699***
Clinical Outcome				
mRS Onset day 30	-0.060	0.639	0.065	0.614***

****Spearman test*

Discussion

The incidence of stroke in this study was higher in males (54%) compared to females (46%), which is consistent with data from the 2018 Results of the Basic Health Research report in Indonesia, where stroke occurrence was also higher in males (11%) than females (10.9%) (12). This finding is supported by previous study that found a higher prevalence of stroke in males across 18 hospitals in Indonesia. Despite the higher incidence of stroke in males, studies suggest that the risk of stroke is actually greater in females, particularly post-menopause, and the use of oral contraceptives also increases stroke risk in women (13). Age is another significant risk factor for stroke, with older age being non-modifiable (7). In this study, most ischemic stroke patients were between the ages of 44-59 years (54%), similar to study in Shandong, which reported an average age of 61.4±8.9 years for patients with favourable outcomes, and 61.7±9.6 years for those with unfavourable outcomes. These results align with the established understanding that older age is the highest non-modifiable stroke risk factor, associated with higher morbidity and mortality rates (14). The levels of ICAM-1 in patients with acute ischemic stroke were found to be higher than in the subject controls, though the difference was not statistically significant ($p > 0.05$). This observation is consistent with previous findings, who reported a significant increase in ICAM-1 levels during the acute phase of ischemic stroke, particularly in patients with more severe neurological deficits (15). ICAM-1 plays a critical role in mediating inflammatory responses by facilitating leukocyte adhesion to the vascular endothelium and promoting their transmigration, which exacerbates cerebral injury through the formation of edema and increased vascular permeability. However, the lack of statistical significance in the present study may be attributed to sample size limitations or individual variability in ICAM-1 expression among patients (6). No significant correlation was observed between ICAM-1 levels and stroke severity as measured by NIHSS scores, or with clinical outcomes based on mRS scores at discharge. These findings align from Chongqing Stroke Study, who similarly found no association between ICAM-1 levels and stroke severity across mild, moderate, and severe cases (7,16). Conversely, another study that reported that elevated ICAM-1 levels were predictive of worse outcomes, suggesting that methodological differences, such as timing of blood sample collection or population characteristics, might account for the discrepancy (7,17). There is no clear consensus regarding serum ICAM-1 levels in patients with acute ischemic stroke compared to healthy individuals. Thus, while there are indications that ICAM-1 levels may differ between these groups, a definitive consensus on normal values and their clinical implications has yet to be established through further research. Variations in ICAM-1 levels across studies are largely influenced by the laboratories and assays used for measurement, as well as other variables that may affect the results. Therefore, it is crucial to take all these variables into account when interpreting test outcomes (7,16). Platelet counts in stroke patients were lower than in subject controls, although this difference was not statistically significant ($p > 0.05$). This result is consistent with findings from France, who attributed reduced platelet counts during the acute phase of stroke to platelet consumption in the context of thrombus formation and vascular injury (18). Further emphasized the dual role of platelets in stroke pathology, noting that both low and high platelet counts can influence outcomes via mechanisms of thrombosis and inflammation (19). These findings underscore the complexity of biomarker interactions in acute ischemic stroke. While ICAM-1 and platelet count are implicated in inflammatory and thrombotic pathways, their individual contributions to stroke severity and outcomes may be influenced by a range of other factors, including additional inflammatory mediators like TNF-α, interleukins, and adhesion molecules such as VCAM-1 (20).

Conclusion

In conclusion, this study found that ICAM-1 levels and platelet count may not reliably indicate stroke severity or predict clinical outcomes during the acute phase. Additionally, long-term studies are required to assess whether changes in ICAM-1 levels and platelet count over time correlate with recovery or post-stroke complications. Expanding research to include more diverse populations and evaluating long-term outcomes, such as functional recovery or mortality, could provide more conclusive evidence regarding the clinical relevance of ICAM-1 and platelet count in stroke management.

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Conflict of Interest: Each author declares that he or she has no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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