Platelet Lymphocyte Ratio (PLR) as a Predictor of In-Hospital Outcomes Among Acute Ischemic Stroke (AIS) Patients in a Tertiary Hospital

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ABSTRACT

Introduction

Acute Ischemic Stroke (AIS) is a medical emergency that affects people globally. In the Philippines, it remains as the third leading cause of mortality. This study aims to determine the use of platelet-lymphocyte ratio (PLR) - a simple, economical, and safe tool - as a predictor of in-hospital outcomes in patients with acute ischemic stroke.

Methods

A retrospective cross-sectional study was conducted among AIS patients at the Remedios Trinidad Romualdez Hospital (RTRH) Tacloban City, Leyte, Philippines from January 2020 to December 2022. Clinical demographics, laboratory profile, and hospital outcomes were described. Descriptive statistics, Mann-Whitney test, and T-test were utilized to determine the association between PLR and in-hospital outcomes.

RESULTS AND CONCLUSION

There were 76 patients enrolled in the study, majority were females (57.9%), and hypertensive (84.2%). Risk factors that are pivotal to the development of AIS were also identified. To note, half of the population presented with unilateral body weakness. Moreover, only 7.9% died due to the disease. Higher PLR levels resulted from an increased platelet count and a decreased lymphocyte count. However, no significant association between PLR levels and AIS outcomes was noted, hence the need for further investigation of these parameters.

Keywords: *Acute Ischemic Stroke, Platelet-lymphocyte ratio, In-hospital outcomes*

INTRODUCTION

Background of the study

Cerebrovascular diseases include ischemic and hemorrhagic strokes, which are both common and highly debilitating. Stroke is the 2nd leading cause of death with 6.2 million recorded deaths in 2015 worldwide[1]. In the Philippines, stroke is considered the third leading cause of death next to heart disease and cancer with a crude death rate of 58.1 per 100,000 (or 60,277 deaths)[2]. Unfortunately, thirty-six percent (36%) of the total stroke deaths are not seen nor attended to by any medical personnel due to challenges in our local health system.

Acute ischemic stroke (AIS) is characterized by sudden cessation of blood flow to a specific region of the brain lasting for a few minutes [1], which may be with or without signs of disability, or even death[3]. Clinical manifestations of stroke would include a change in vision, gait, or ability to speak or understand, sudden, severe headache, or hemiparesis[1]. Central to the pathogenesis of stroke is inflammation, which can be detected readily by Computed Tomography (CT) of the brain. Moreover, previous studies suggest that the use of inflammatory markers may have strong independent prediction values for stroke outcomes[4]. A novel and inexpensive inflammatory marker such as platelet-to-lymphocyte ratio (PLR) which can be easily

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obtained from a CBC panel of admitted patients has been applied for predicting inflammation and mortality in many diseases - even in stroke. Previous studies observed that decreased lymphocyte counts were correlated with poor functional outcomes in acute cerebral infarction. Platelets, likewise, have a key role in thrombogenesis and inflammation; however, the relationship between elevated platelet counts and the clinical prognosis is yet to be investigated[5].

This study aims to identify the significant PLR levels in predicting in-hospital outcomes of patients with acute ischemic stroke and its implications, to guide physicians in the local setting with their management, prognostication, and possible long-term goals.

METHODOLOGY

Research design

A retrospective cross-sectional study will be conducted at the RTRH, a 100-bed tertiary private training hospital in Tacloban City, Leyte, Philippines.

Participants

Inclusion criteria

All adult patients meeting the following criteria are included in the study:

- 19 years of age or older
- Diagnosed acute ischemic stroke patients detected on cranial CT scan admitted at RTRH starting January 2020 – December 2022.

Exclusion criteria

- Patients whose cranial CT scan revealed cerebrovascular bleed/hemorrhage.
- Confirmed AIS patients whose charts are lacking vital information pertinent to the research.
- Confirmed AIS patients with liver or kidney failure, blood dyscrasias/ cancer, received end vascular thrombectomy, and a systemic immune disease whose platelet and lymphocyte counts may be erroneously altered.

Data Collection Process

Patients who are diagnosed with acute ischemic stroke will be identified through the in-patient census. Charts of patients who met the eligibility criteria for the study will be retrieved from the institution's medical records department to extract their demographics, history, comorbidities, the course in the wards, and imaging (Cranial CT Scan) and laboratory results. Patients will be screened for inclusion and exclusion criteria previously mentioned.

To calculate the PLR (Platelet to lymphocyte ratio), CBC (Complete Blood Count) tests performed by fully automated hematology analyzer taken just after admission (before starting any treatment) will be reviewed. Total platelet count will be divided by the total lymphocyte count and the quotient will then be compared with the reference value set from a previous study done by Sharma and Gandhi, 2021.

Finally, the in-hospital outcomes of the patients will be tagged as discharged or mortality.

Data analysis

Nominal data will be expressed in frequency counts and percentages. Then, the Chi-Square Test and Fisher's Exact Test of independence will be used to test the association between in-hospital adverse outcomes and each categorical variable. A p-value of less than 0.05 will be considered significant.

RESULTS

Table 1 reveals valuable insights into the clinical, demographic, and laboratory characteristics of patients diagnosed with Acute Ischemic Stroke (AIS) in this study. The average age of AIS patients was approximately 67 years, with a variation of around 12 years. Females (57.9%) had a higher incidence of AIS compared to males (42.1%). The most common co-morbidities were hypertension (84.2%), diabetes mellitus (52.6%), and dyslipidemia (26.3%). 25% of the population were current smokers and 17.1% had a

Table 1. Clinico-demographic and Laboratory Characteristics of AIS Patients

Characteristics	Total (N = 76)
Age, Years, mean ± SD	66.91 ± 11.68
Female, n (%) Male, n (%) Hypertension, n (%) Diabetes Mellitus, n (%) Dyslipidemia, n (%)	44 (57.9) 32 (42.1) 64 (84.2) 40 (52.6) 20 (26.3)
Current smoking, n (%)	19 (25.0)
Family History of AIS, n (%)	13 (17.1)
Body weakness, unilateral n (%) Slurred speech n (%)	37 (49) 28 (37)
Platelet CT, mean ± SD	272.22 ± 77.54
Lymphocyte CT, mean ± SD	20.58 ± 9.63
PLR, mean ± SD Discharged, n (%)	181.08 ± 89.80 70 (93.1)
Mortality, n (%)	6 (7.9)

Table 2. Comparison of the characteristics between subgroups based on the PLR

Characteristics	Low PLR N = 23 (PLR < 126.67)	High PLR N = 53 (PLR > 126.67)	p-value
Age, Years, mean ± SD	64.83 ± 12.49	67.81 ± 11.32	0.331
Male, *n (%)*	11 (47.8)	21 (39.6)	0.509
Female, *n (%)*	12 (52.2)	32 (60.4)	
Current smoking, *n (%)*	4 (17.4)	15 (28.3)	0.316
Family History of AIS, *n (%)* Hypertension *n (%)* Body weakness, unilateral *n (%)*	5 (21.7) 18 (23.7) 9 (11.8)	8 (15.1) 46 (60.5) 28 (38.8)	0.483 - -
Platelet CT, mean ± SD	236.04 ± 63.93	287.92 ± 78.18	0.004*
Lymphocyte CT, mean ± SD	26.52 ± 9.04	18.0 ± 8.76	0.000*
Disposition, *n (%)*	2 (8.7)	4 (7.5)	0.798

**P values less than 0.05 were considered statistically significant*

significant family history of acute ischemic stroke. 49% of the subjects presented with unilateral body weakness (either right or left) while 37% came in due to slurred speech. Additionally, the mean Platelet-to-Lymphocyte Ratio (PLR) was found to be around 181. Finally, majority of the patients (93.1%) were discharged, while 6 succumbed to AIS.

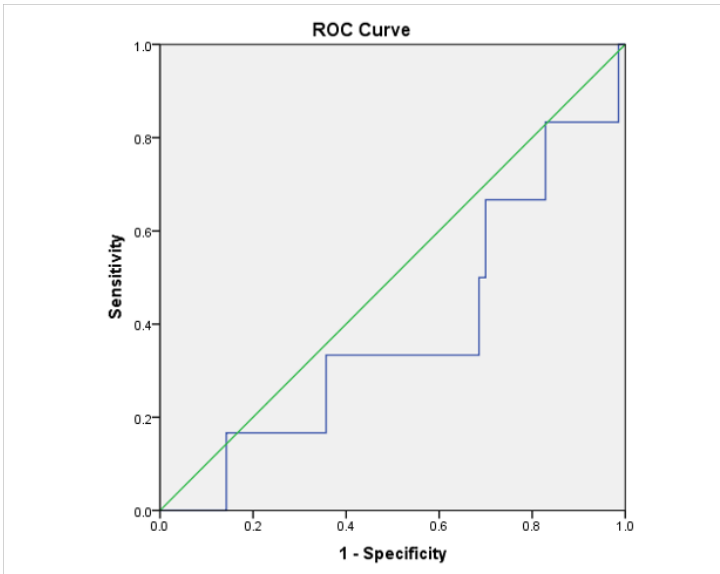
This table shows the analysis of demographic and clinical characteristics, focusing on parameters with a significance level of $P < 0.05$ in univariate analysis, was presented in Table 2. The study revealed distinct differences between patients categorized into high and low Platelet-to-Lymphocyte Ratio (PLR) groups. Notably, individuals with high PLR exhibited a statistically significant increase in platelet count ($P = 0.004$) and a concurrent decrease in lymphocyte count ($P = 0.000$).

In the univariate analysis, the dependent variable considered was the disposition (discharged, mortality) of individuals. Table 3 outlines the results of the multivariate logistic regression analysis after adjusting for confounding factors, focusing on the relationship between several variables—Platelet-to-Lymphocyte Ratio (PLR), platelet count (platelet CT), and lymphocyte count (lymphocyte CT)—and the occurrence of Acute Ischemic Stroke (AIS) in patients.

Table 3. Multivariate logistic regression analysis of the associations between PLR and AIS Patients

	B	S.E.	Wald	p-value	Adjusted Odds Ratio	Adjusted Odds Ratio (95% C.I.)	
						Lower	Upper
Platelet CT	-0.012	0.007	2.526	0.112	0.988	0.974	1.003
Lymphocyte CT	-0.028	0.067	0.170	0.680	0.973	0.853	1.109
PLR	-0.090	1.194	0.006	0.940	0.914	0.088	9.484
Constant	1.017	1.602	0.403	0.525	2.766		

Figure 1: The receiver operating characteristic (ROC) curve analysis of platelet-to-lymphocyte ratio for predicting AIS patient.



DISCUSSION

Acute Ischemic stroke (AIS) is a medical emergency caused by a decreased blood perfusion to the central nervous system which ultimately results in brain cell death and unfavorable outcomes[6].

The highest burden of disease is shared by low- and middle-income countries worldwide, increasing therefore the gap in appropriate identification and treatment.

Across studies, it has been established that stroke arises from various risk factors either modifiable (smoking, diet, and physical inactivity), or non-modifiable (age, sex, family history, race/ethnicity)[7]. O'Donnell *et al* (2010) further emphasized in the INTERSTROKE case-control study that 90% of the risk factors are modifiable, spanning from the presence of co-morbidities, poor lifestyle habits, an increased waist-to-hip ratio, stress and depression, and biochemical disturbances like the ratio of apolipoprotein B to A1[8].

Several risk factors for developing AIS were also identified in our study. The mean age for AIS occurrence was 67 years old which was comparable to a study by Kobina *et al* (2021). They noted that the mean age of onset of first stroke in males was 61.47 ± 13.36 years and in females at 63.41 ± 15.41 years[9]. Disability as an outcome of the stroke event may be detrimental to this population since people usually retire at this age, leaving them with health, emotional, and financial burdens. Differences in sex have also been identified as an important risk factor Worldwide, the lifetime risk of stroke (from age 25 years onward) is higher in women (25.1%) than in men (24.7%). To add, the highest lifetime AIS risk in East Asian women is 36.3%[10]. This supported our finding of a higher incidence of female AIS patients compared to males. Yoon et al (2023) proposed that women have unique risk factors such as pregnancy, endogenous hormone levels, and exogenous hormone therapy which could aggravate the development of AIS[11]. However, other studies claim that male risk factors are far more common and contributory e.g. testosterone hormone effects that constrict the endothelial and decrease blood flow, higher cigarette use, and lifestyle. Nevertheless, the incidence of AIS has been increasing in both sexes, hence, it should be considered in optimal risk assessment to tailor preventive strategies for both[12].

In addition, the presence of co-morbidities was linked to developing AIS. We demonstrated that the most common co-morbidities in this population were hypertension, followed by diabetes mellitus, then dyslipidemia. She et al (2022) noted similar results wherein 74.7% were hypertensive, 28.5% were diabetic and 23.3% were dyslipidemic. Coronary artery disease (19.1%) and obesity (17.7%) were also contributory[13]. In general, hypertension is related to high levels of Angiotensin II and AT1R activation in the brain and blood vessels. This leads to an increased superoxide production and decreased function of nitrogen oxide (NO) – a potent vasodilator. During AIS, the increased vasoconstriction and smaller lumen diameters of cerebral arteries and arterioles can potentiate perfusion deficit and impair collateral flow, resulting in infarct progression [(14)].These findings underscore the essence of identifying and controlling co-morbidities to prevent adverse outcomes and long-term morbidity.

Additionally, this study explored lifestyle factors, indicating that one in every four AIS patients was a smoker, highlighting the potential role of smoking in contributing to AIS cases. Studies performed across various ethnicities and populations demonstrated that current smokers have at least a two- to fourfold increased risk of stroke. In contrast, lifelong nonsmokers or individuals who had quit smoking more than 10 years prior have a lesser risk. Numerous factors such as elevated platelet aggregability, reduced HDL cholesterol, elevated fibrinogen levels, and direct toxic effects of 1,3-butadiene - a vapor phase component of ambient tobacco smoke that has been demonstrated to hasten atherosclerosis— are likely responsible[15].

Blaz et al (2023) described the prevalence of a family history of AIS in stroke-free individuals (37%) versus patients with ischemic stroke (52%)[16]. Comparably, it was found in our study that one in every six patients had a family history of AIS, suggesting a genetic component in some instances, hence the importance of early screening and adequate counseling to high-risk individuals.

Notably, a substantial portion of AIS cases presents unilateral body weakness (50% of the population), underscoring the impact on motor functions. Additionally, slurred speech is observed in a notable 37% of the population, highlighting the involvement of language-related neural pathways. Similarly, Mosley *et al* (2014) reported limb weakness (67%), speech problems (57%), and facial weakness (24%) as the most frequent symptoms[17]. This demonstrates the negative impact on the patient's quality of life. Ultimately, the role of primary prevention in addressing these aspects, cannot be overemphasized especially those that pose a greater risk of a first stroke event[7].

Several studies on prognostic tools for AIS have been published over the years – recently the platelet-to-lymphocyte ratio (PLR) which has also been used in other inflammatory states. It is particularly promising as it is quick, safe, and economical and may shed light on both inflammatory and thrombotic or hemostatic pathways that are assumed to be involved in the pathophysiology of AIS[18]. In 2021, a case-control study presented that poor outcomes after ischemic stroke were associated with high PLR. The risk of mortality increased to 4 to 5 times when the PLR value was>145[19]. Additionally, in a study by Yan et. al, 2021, they concluded that excessive platelet activation and accumulation may result in worse clinical outcomes after an acute ischemic stroke. Higher lymphocytes, on the other hand, may be beneficial due to their neuroprotective function. As a result, hypothetically, a high PLR may result in poorer outcomes following a stroke[20].

The mean Platelet-to-Lymphocyte Ratio (PLR) in our study was found to be around 181, providing a marker for potential inflammation or immune response in AIS patients. Alarmingly, the study observed a mortality rate of one in every 12 AIS patients, with six patients succumbing to the condition. These findings underscore the importance of understanding the diverse characteristics of AIS patients.

Our study also suggests a potential correlation between elevated PLR and alterations in platelet and lymphocyte counts, highlighting the importance of considering these hematological parameters in understanding the clinical profile of individuals with high PLR. Additional exploration of these relationships may contribute valuable insights into the underlying mechanisms and potential implications for patient prognosis or therapeutic interventions.

Furthermore, the adjusted odds ratios (aOR) for PLR, platelet CT, and lymphocyte CT were reported as 0.914 (95% CI: 0.088–9.484, P = 0.940), 0.988 (95% CI: 0.974–1.003, P = 0.112), and 0.973 (95% CI: 0.853–1.109, P = 0.680), respectively, indicating that these variables were not found to be significantly associated with AIS. Subsequently, Receiver Operating Characteristic (ROC) analysis was conducted, revealing a best cutoff level for PLR at 182.95 (P = 0.345) with a sensitivity of 0.333 and specificity of 0.357. The area under the ROC curve was 0.383 (95% CI: 0.145–0.622), suggesting limited discriminative ability in predicting AIS based on PLR. These findings contribute to the understanding of the potential associations between hematological parameters and AIS risk, emphasizing the need for further research and exploration in this domain.

Overall, this comprehensive data interpretation contributes to a better understanding of the clinical characteristics and associated factors in AIS patients, facilitating targeted interventions and preventive strategies.

CONCLUSION

There were 76 patients included in the study, predominantly females (57.9%), and hypertensive (84.2%), with a mean age of 67 years. Risk factors such as smoking history, family history of AIS, and presence of comorbidities were noted. The most common symptom was unilateral body weakness (50%) and only 7.9% succumbed to the disease.

An increased platelet count and a decreased lymphocyte count resulted in higher PLR levels. However, no significant association between PLR levels and AIS outcomes was noted, hence the need for further investigation of these parameters.

LIMITATIONS

Because of the study's retrospective nature, only associations, not causal relationships, could be investigated. Furthermore, neurological functional scales such as NIHSS and Modified Rankin Scores were not employed to limit additional confounding variables.

RECOMMENDATIONS

We recommend a prospective cohort study with other variables to be included such as the functional status of the patient upon admission and discharge, the location and extent of the infarct, and the individual evaluation of platelet and lymphocyte which could all be contributory to an AIS patient's disposition.

ACKNOWLEDGMENT

The authors would like to acknowledge the efforts of the people who contributed to the fulfillment of this research.

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DISCLAIMER

This research was done at the Remedios Trinidad Romualdez Hospital (RTRH) in Tacloban City, Leyte. To date, there are no conflicts of interest to this study such as having been presented in a conference or appearing in any other journal.

Appendix A. Sample Data Collection Form

PATIENT NO._____

I.**DEMOGRAPHIC PROFILE**	
NAME (OPTIONAL)	
AGE	☐ 19-59 y.o ☐ ≥ 60 y.o.
SEX	☐ Male ☐ Female
ADDRESS:	
SIGNS AND SYMPTOMS	☐ Asymptomatic ☐ Body Weakness ☐ Change in ability to speak ☐ Change in ability to understand ☐ Change in vision ☐ Deceased/absent sensation ☐ Dizziness ☐ Dysphagia ☐ Headache ☐ Incoordination ☐ Nausea/Vomiting ☐ Slurred speech ☐ Others _____
CO-MORBIDITY	☐ Hypertension ☐ Diabetes Mellitus ☐ Dyslipidemia ☐ Atrial Fibrillation ☐ Cerebrovascular Disease ☐ Chronic Kidney Disease ☐ Others _____
SMOKING HISTORY	☐ Non-smoker ☐ Smoker
FAMILY HISTORY OF AIS	☐ Present ☐ Absent
II.**BIOCHEMICAL MEASUREMENT**	
WHITE BLOOD CELL COUNT PLATELET COUNT LYMPHOCYTE COUNT COMPUTED PLATELET LYMPHOCYTE RATIO (PLR)	_____ _____ _____ _____
PLATELET LYMPHOCYTE RATIO (PLR)	☐ Low ☐ Normal ☐ High
DISCHARGE DISPOSITION	☐ Discharged ☐ Mortality