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Red cell distribution width (RDW) Level as one of the Alternative Diagnostic Tools in Stroke Patients

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Abstract

Background: Stroke is an emergency that requires prompt treatment. Non-contrast head computed tomography (CT) is the preferred imaging modality for diagnosing stroke due to its accessibility and speed, but it's not always available. There are many alternative diagnostic scales for stroke, such as the Siriraj and Gadjah Mada scores, but their specificity remains low. In stroke patients, inflammation increases oxidative stress and is thought to increase Red cell distribution width (RDW).

Objective: To evaluate the accuracy of RDW as an alternative diagnostic method in stroke patients.

Methods: This cross-sectional study examined secondary data from the medical records of 120 stroke patients at Al-Ihsan Regional Hospital in June-August 2024. Inclusion criteria were stroke patients who underwent RDW and CT scans. Patients who were previously diagnosed with stroke, with anemia or with a history of anemia, and patients with hemolytic disorders were all excluded.

Results: RDW levels in ischemic stroke were higher and statistically significant with a z score = 4.68, and a p value < .00001.

Conclusion: The RDW value can be considered an alternative diagnostic tool for determining stroke in remote areas.

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INTRODUCTION

Strokes are the world's second greatest cause of mortality, accounting for around 5.5 million fatalities annually. Stroke causes not just significant mortality but also severe morbidity, with up to half of survivors permanently handicapped[1]. Strokes are one of the leading causes of mortality and disability in Indonesia. Indonesia has the highest age- and gender-standardized death rate and the highest number of life years lost due to disability when compared to other South East Asian countries[2]. According to the American Heart Association (AHA), the definition of intracerebral hemorrhage is brain injury resulting from acute extravasation of blood into the brain parenchyma due to rupture of blood vessels[3].

Because it is quick and easy to use, non-contrast head CT is the recommended imaging technique for stroke diagnosis. CT can differentiate between intracranial pathologies, such as subarachnoid hemorrhage, ischemic stroke, and intracerebral hemorrhage (ICH), and can reveal the extent of hemorrhage. Brain imaging in ischemic stroke is recommended before undertaking specific therapy[4]. Many types of diagnostic scales have been developed for the diagnosis of stroke, both ischemic and hemorrhagic. This diagnostic scale is useful for increasing diagnostic accuracy, supporting decision-making in stroke management, and reducing variability in clinical trials of stroke interventions. For example, the Siriraj and Gadjah Mada scores, but their accuracy in diagnosing stroke, infarction, and hemorrhage still has low specificity[5].

Ischemic stroke causes cell inflammation. Inflammatory cytokines cause increased oxidative stress. Plasma inflammatory indicators, including interleukin-6 (IL-6), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP), are positively correlated with RDW. Higher RDW values, even though they are still within the normal range, can worsen the inflammatory conditions in stroke, causing poor clinical outcomes. In stroke patients, elevated RDW may indicate elevated inflammation and can be a marker of pro-thrombotic conditions that increase in ischemic stroke[6]. According to a prior study, ischemic stroke patients' average RDW was higher than the normal value (15.39)[7]. Meanwhile, for hemorrhagic stroke patients, the result of research stated that the average RDW was 14.02[8]. Based on this, researchers were interested in measuring the accuracy of RDW as an alternative diagnostic tool.

METHODS

Medical records provided the research data for this cross-sectional investigation. Patients with RDW levels more than 14.5 are considered to have increased RDW. The subjects in this study were all patients at Al-Ihsan Regional Hospital, both outpatients and inpatients, who were diagnosed with stroke, ischemic and hemorrhagic, who underwent RDW examinations and CT scan exams recorded in personal medical records kept by the medical records division of Al-Ihsan Regional Hospital in June-August 2024. On the other hand, patients who were previously diagnosed with a stroke, patients with anemia or a history of

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anemia, and patients with hemolytic disorders were all excluded. The sample size formula used is the Woodward analytical cross-sectional formula.

RDW levels were the study's independent variables. In the meantime, the dependent variable was determined to be stroke diagnosis. Data analysis used the Mann-Whitney for numerical data and the Chi-square test for categorical data to find relationships between variables. All data were analyzed using SPSS.

The implementation of this research was preceded by permission from the Research and Ethics Committee of Al Ihsan Regional Hospital to access patient medical records stored by the medical records division of Al Ihsan Regional Hospital, with number 5931/70/ KEPK-RSUD.Al.Ihsan/VII/2024.

RESULTS

As shown in Table 1, there were 96 ischemic stroke patients. The mean age of patients in this study was 60.1 years, with a standard deviation of 12.1 years. From a gender standpoint, it showed that cases of ischemic stroke were dominated by men, namely 53.9% (51 people), while the number of men was 46.1% (45 people). The majority of patients had risk factors for hypertension, totaling 77 cases (80.2%), and diabetes, totaling 30 cases (31.25%).

Classification based on the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) was highest in 71 cases (65.6%) due to small artery occlusion, followed by large artery occlusion in 17 cases (17.8%) and cardioembolism in 9 cases (9.4%).

Table 1. Characteristics of Patients with Ischemic Stroke

No	Variables	Frequency/n	Percentage (%)
1	Age (year), Mean±SD	60,1±12,1	
	Age (year), Median (min-max)	60,1 (25,0-88,0)	
2	Gender		
	Male	51	53,1
	Female	45	46,9
3	TOAST Classification		
	Large-artery atherosclerosis	17	17,8
	Cardioembolism	9	9,4
	Small-vessel occlusion	63	65,6
	Stroke of another determined etiology	6	6,25
	Stroke of undetermined etiology	0	0
4	Risk Factors		
	Hypertension	77	80,2
	Type 2 Diabetes	30	31,25
	Dyslipidemia	25	26,04
	Hyperuricemia	7	7,3
	Smoking	15	15,63
	Coronary heart disease	11	11,46
	Arrhythmia	7	7,3
	Heart failure	7	7,3

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Patients with hemorrhagic stroke in this research had an average age of 59 years, as shown in Table 2, with a standard deviation of ±10.69, and cases of hemorrhagic stroke were dominated by men, namely 54% (13 people), while the number of women was 46% (11 people). The most common location of hemorrhage in this study was non-lobar (basal ganglia). This study identified hypertension to be the most frequent risk factor in hemorrhagic stroke patients.

The average RDW in ischemic stroke patients in this study was 14,99. Meanwhile, the average RDW in intracerebral hemorrhage patients in this study was 13.95. As attached in Table 3, a chi-square test of independence was performed to examine the relation between increased RDW and ischemic stroke diagnosis. The relation between these variables was significant, X2 (1, N = 120) = 26.89, p-value = 0,00001 ($p < 0.05$). Ischemic stroke patients were more likely than hemorrhagic stroke patients to have increased RDW levels.

As shown in Table 4, 96 patients with a diagnosis of ischemic stroke (mean = 14.99, standard deviation = 1.15), compared with 24 patients with hemorrhagic stroke (mean = 13.93, standard deviation = 0.97), found that CV RDW levels in ischemic stroke were higher and statistically significant with a t value = 4.68 and a p-value < .00001 ($p < 0.05$).

Table 2. Characteristics of Patients with Hemorrhagic Stroke

No	Variables	Frequency/n	Percentage (%)
1	Age (year), Mean±SD	58,91±10,69	
	Age (year), Median (min-max)	58,91 (21-84)	
2	Gender		
	Male	13	54,16
	Female	11	45,84
3	Location of hemorrhage		
	Basal Ganglia	9	37,5
	Lobar	6	25
	Thalamus	3	12,5
	Internal capsule	1	4,17
	Pons	3	12,5
	Cerebellum	2	6,25
4	Risk Factors		
	Hypertension	21	87,5
	Smoking	5	20,8
	Dyslipidemia	7	29,17
	Usage of anticoagulant and/or antiplatelet	4	16,7
	Alcohol consumption	1	4,16
	Chronic kidney disease	3	12,5

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Table 3. Chi-Square Analysis of RDW levels in Stroke Patients

RDW Level	Ischemic stroke diagnosis (%)	Hemorrhagic stroke diagnosis (%)	Total (%)	x	p	Sensitivity (%)	Specificity (%)	Positive LR
Increased	71	4	75 (62,5)	26,89	< 0.00001	74	83,3	4,43
Not increased	25	20	45 (37,5)					
Total	96 (80)	24 (20)	120 (100)					

Table 4. Mann-Whitney Analysis of RDW Levels in Stroke Patients

Variables	n	Mean	Z score	P < 0,5
Mean RDW CV				
Ischemic stroke	96	14,99	4.68	< .00001
Hemorrhagic stroke	24	13,95		

DISCUSSION

The mean age of patients in this study was 60.1 years, with a standard deviation of 12.1 years. This is similar to a study that concluded the older you get, the higher the risk of stroke. These results illustrate that older people are more susceptible to ischemic stroke than younger people. This is related to the degenerative theory, which causes changes in the structure and function of blood vessels, such as lumen diameter, wall thickness, wall strength, and endothelial function, which underlie atherosclerosis[9].

The results of the study showed that cases of ischemic stroke were dominated by men, namely 53.9% (51 people), while the number of men was 46.1% (45 people). This is similar to the results of a study that revealed risk factors, including smoking, high cholesterol, peripheral artery disease, and coronary artery disease, are more common in males. According to research, women tend to have a decreased risk of stroke and enjoy neuroprotective benefits associated with the hormone estrogen prior to menopause between the ages of 40 and 75 compared with men[9].

Small artery occlusion was found to be the highest type of ischemic stroke, totaling 71 cases (65.6%). A Previous study conducted in 2014 also showed that a small-vessel occlusion was the most common type of ischemic stroke in Asia. Asians are more likely to have a small-vessel blockage, which may be partially explained by their comparatively high consumption of salt and a high rate of uncontrolled hypertension[10].

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The majority of ischemic stroke patients in this study had risk factors for hypertension, totaling 77 cases (80.2%). A study conducted in 2020 found that the most common risk factor in ischemic stroke patients was hypertension[11]. Atherosclerotic plaques and platelet aggregation from detached endothelium can result from hypertension-induced thinning of blood vessel walls and vascular damage. Ischemic stroke can result from these atherosclerotic plaques blocking blood arteries in the brain[12].

The mean age of hemorrhagic stroke patients in this study was 59 years, with a standard deviation of ±10.69. Previous research revealed that aging is an unstoppable process that heightens the risk of hemorrhagic stroke. Age-related increases in the prevalence of aneurysms, atherosclerosis, and hypertension may have a role in the development of hemorrhagic stroke[13].

The results of the study showed that cases of hemorrhagic stroke were dominated by men, namely 54% (13 people), while the number of women was 46% (11 people). This sex-related difference in hemorrhagic stroke incidence may be explained by hormonal changes, genetics, lifestyle variations, and behavioral risk factors, including men's greater propensity for alcoholism and cigarette smoking[14].

The most common location of hemorrhage in this study was non-lobar (basal ganglia). A 2017 study also stated that the most common site of hemorrhage was non-lobar (putamen)[15]. The main cause of hemorrhage is chronic hypertension. Vascular remodeling at the cellular level, driven by high arterial pressures, results in lipohyalinosis and genuine arteriolar dissections (Charcot-Bouchard aneurysms), which rupture, allowing high-pressure blood to extravasate into the deep parenchyma. The putamen, caudate, thalamus, brainstem, and deep cerebellar nuclei are among the deep brain regions that receive blood from tiny capillaries and are prone to hypertensive hemorrhages [16].

In this study, hypertension was found to be the most common risk factor in stroke patients. A study conducted in 2018 also showed similar results. Vascular alterations brought on by chronic hypertension include microaneurysm formation, luminal narrowing, microhemorrhage, and fibroid necrosis (lipohyalinosis) in the white matter supplied by penetrating arteries and arterioles, all of which are prone to rupture [17].

The average RDW in ischemic stroke patients in this study was 14.99. This result is consistent with a study that found the average RDW in ischemic stroke patients exceeded the normal value (14.7)[18].

Several studies have revealed that RDW levels are higher in individuals with cardiovascular disease, which includes ischemic stroke. Even in people who do not have risk factors such as atrial fibrillation, heart failure, or coronary heart disease, RDW levels still increased in ischemic stroke patients[19].

Ischemic stroke causes cell inflammation. Inflammatory cytokines cause increased oxidative stress. Plasma inflammatory indicators, including interleukin-6 (IL-6), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP), are positively correlated with RDW. Inflammatory processes occur in ischemic stroke and cause impaired erythropoiesis. An increase in pro-

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inflammatory markers, specifically IL-6, indicates inflammation. This will lead to anisocytosis as immature erythrocytes are released into the bloodstream, raising RDW values and causing erythrocyte damage, increased fragility, and disruption of erythrocyte maturation. Inflammation and oxidative stress can disrupt erythropoiesis, inhibiting red blood cell maturation, causing anisocytosis, and leading to higher RDW in patients. An imbalance between in vivo oxidation and antioxidant defenses causes oxidative stress, leading to increased protease production, neutrophil infiltration, and accumulation of substantial quantities of oxidative intermediates. One of the main causes of aging and illness is oxidative stress, the detrimental effects of free radicals in the body. Red blood cell viability may be affected by oxidative damage to proteins, lipids, and nucleic acids caused by an imbalance between antioxidants and oxidants. The RDW number will rise as a result of this condition's damage to the red blood cell membrane, increased fragility, decreased maturation, and increased red blood cell age [20,21].

Meanwhile, the average RDW in intracerebral hemorrhage patients in this study was 13.95. Previous research also found the mean RDW to be 13.8 (not increased)[22].

A chi-square test of independence was performed to examine the relation between increased RDW and ischemic stroke diagnosis. RDW was categorized as increased (>14.5) and not increased (<14.5). The relationship between these variables was significant, X2 (1, N = 120) = 26.89, p = 0.00001 (p < 0.05). Ischemic stroke patients were more likely than hemorrhagic stroke patients to have increased RDW levels.

96 patients with a diagnosis of ischemic stroke (mean = 14.99, standard deviation = 1.15) compared with 24 patients with hemorrhagic stroke (mean = 13.93, standard deviation = 0.97) found that RDW CV levels in ischemic stroke were higher and statistically significant with a t value = 4.68 and a p value < .00001 (p < 0.05).

The difference in RDW levels between ischemic and hemorrhagic stroke is most likely due to the fact that ischemic stroke patients have more factors that can raise their RDW, including coronary artery disease, atherosclerosis, atrial fibrillation, and heart failure[23,24]. On the other hand, hemorrhagic stroke patients have fewer mechanisms[25] that will lead to an increase in RDW, namely hypertension[26] and smoking[27].

Increased RDW levels can be used as a predictor of atrial fibrillation[23]. Given that erythrocytes both transport oxygen to tissues and play a significant role in cardiovascular regulation by releasing extracellular nucleotides and other mediators, it appears likely that alterations in erythrocyte function will have a direct impact on the heart[28]

A cohort study conducted in 2018 identified elevated RDW levels in subjects diagnosed with a heart attack[23]. Erythrocytes contain high amounts of free cholesterol, and pathological changes in the erythrocyte membrane can lead to erythrocyte accumulation within the atheromatous plaque. By distributing the inflammatory cascade and releasing free cholesterol onto atherosclerotic plaques, the erythrocyte membrane promotes atherosclerosis by supplying lipid-rich membranes that support foam cell growth. Plaque

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destabilization is encouraged by erythrocyte buildup[29].

Numerous studies have shown that RDW is an independent predictor of heart failure incidence [23]. Heart failure is linked to the activation of both cellular and cytokine-mediated inflammatory pathways, which can compromise bone marrow function, resulting in the premature release of erythrocytes into the bloodstream [30].

CONCLUSION

Increased RDW values were more commonly found in patients diagnosed with ischemic stroke. This is because in ischemic stroke patients, there are more mechanisms that will lead to an increase in RDW. The RDW value can be considered a marker for differentiating and diagnosing stroke. The results of this research can be used by clinicians to have a grasp of the clinical picture of patients with stroke, ischemic, and hemorrhagic. It is also hoped that the RDW value can be considered one of the alternative diagnostic scales used alongside the Siriraj Score and Gadjahmada Algorithm to determine the diagnosis of stroke in remote areas without CT scans.

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