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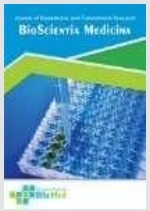

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The Double Inflammatory Burden: Red Cell Distribution Width as an Exploratory Biomarker for Functional Outcome in Ischemic Stroke with Comorbid Systemic Lupus Erythematosus

Resita Indah Sukraputri[1*], Endang Kustiowati[2], Hexanto Muhartomo[2], Dodik Tugasworo[2], Aris Catur Bintoro[2], Elta Diah Pasmanasari[2]

[1]Specialized Residency Training Program, Neurology Study Program, Faculty of Medicine, Universitas Diponegoro/Dr. Kariadi General Hospital, Semarang, Indonesia

[2]Senior Lecturer Staff, Department of Neurology, Faculty of Medicine, Universitas Diponegoro/Dr. Kariadi General Hospital, Semarang, Indonesia

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***Corresponding author:**
Resita Indah Sukraputri

E-mail address:
Resitaindahs@gmail.com

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A B S T R A C T

Background: Ischemic stroke in patients with systemic lupus erythematosus (SLE) presents a highly unique clinical phenotype characterized by amplified systemic inflammation, profound endothelial dysfunction, and a pervasive prothrombotic state. The combined, synergistic effect of this double inflammatory burden exacerbates acute neuronal injury and leads to significantly poorer clinical recovery. This study evaluated Red Cell Distribution Width (RDW), a widely available surrogate marker of systemic inflammation, oxidative stress, and impaired erythrocyte deformability, as a prognostic biomarker for functional outcomes in this specific, high-risk inflammatory phenotype. **Methods:** In this retrospective analytical pilot study, 34 adult patients diagnosed with acute ischemic stroke and comorbid SLE were analyzed. Admission RDW values, National Institutes of Health Stroke Scale (NIHSS) scores, and 90-day Modified Rankin Scale (mRS) scores were collected. A poor functional outcome was rigorously defined as an mRS score of 3–6. Statistical evaluation included Mann-Whitney U tests, Spearman rank correlation, receiver operating characteristic (ROC) curve analysis, and multivariable logistic regression to adjust for baseline neurological severity. **Results:** RDW demonstrated a statistically significant positive correlation with initial stroke severity (NIHSS; $r = 0.397$; $p = 0.020$) and 90-day functional disability (mRS; $r = 0.711$; $p < 0.001$). The median RDW was significantly higher in patients with poor outcomes compared to those with good outcomes (15.6% versus 13.4%, $p < 0.001$). ROC analysis yielded an excellent Area Under the Curve of 0.89 ($p < 0.001$) with an optimal predictive cut-off established at 13.75%. In multivariable analysis adjusting for baseline stroke severity, an admission RDW of 13.75% or higher remained a strongly associated factor for severe long-term disability (adjusted Odds Ratio: 14.82, 95% Confidence Interval: 1.95–112.45, $p = 0.009$). **Conclusion:** RDW is a promising, inexpensive, and universally available prognostic biomarker that demonstrates a strong association with severe functional disability in ischemic stroke patients with comorbid SLE, accurately reflecting the profound neurotoxic impact of the double inflammatory burden.

1. Introduction

Ischemic stroke continues to rank as a leading cause of long-term functional disability, cognitive impairment, and mortality across the globe.[1] The abrupt disruption of cerebral blood flow triggers a rapid, aggressive, and highly complex pathophysiological cascade. This neurovascular catastrophe encompasses immediate intracellular

energy depletion, massive excitotoxicity mediated by glutamate release, severe intracellular calcium overload, generation of reactive oxygen species, and profound neuroinflammation. While ischemic stroke in the general population is predominantly driven by traditional atherosclerotic and metabolic risk factors such as chronic hypertension, dyslipidemia, and diabetes mellitus, ischemic stroke occurring in patients with systemic lupus erythematosus (SLE) represents a distinctly accelerated and highly inflammatory vascular phenotype.[2] Epidemiological data consistently demonstrate that patients with SLE possess a risk of cerebral ischemia that is more than double that of the general population. Furthermore, these patients often present at a significantly younger age and carry a substantially higher burden of multiple, recurrent, or border-zone cerebral infarctions.

The pathophysiology of acute stroke in the context of SLE is uniquely influenced by a chronically primed immune system. The cerebrovascular environment in SLE is compromised by continuous autoantibody circulation, immune complex deposition within the vascular endothelium, dysregulated complement activation, and accelerated premature atherosclerosis.[3] This pre-existing state of intense immune dysregulation sets the stage for what can be conceptualized as a double inflammatory burden when an acute ischemic event occurs. The acute ischemic cerebral injury naturally mounts its own localized and systemic inflammatory response, characterized by microglial activation and leukocyte infiltration into the brain parenchyma. When this acute, massive inflammatory surge is superimposed upon the chronic, smoldering systemic inflammation inherent to SLE, it creates an exceptionally neurotoxic environment. Consequently, patients with SLE experience a 1.4-fold higher mortality rate and a drastically increased likelihood of severe functional dependency following an acute stroke compared to individuals without autoimmune comorbidities.[4]

Given the aggressive clinical course and the high likelihood of poor recovery in the SLE stroke population, there is a critical and unmet need for accessible, rapidly available, and highly reliable prognostic biomarkers.[5] Such biomarkers are essential to guide early therapeutic stratification, inform aggressive neuroprotective interventions, and facilitate objective, evidence-based communication with patients and their families regarding long-term recovery trajectories.[6] Red cell distribution width (RDW), a routine numerical measure of anisocytosis reported in standard complete blood counts, has recently emerged as a remarkably powerful prognostic indicator across various cardiovascular, pulmonary, and neurological disciplines. RDW mathematically represents the coefficient of variation of erythrocyte volume. While traditionally utilized solely for the differential diagnosis of anemias, contemporary hematological research has established that RDW is highly sensitive to systemic inflammation and oxidative stress.[7]

The mechanistic link between inflammation and elevated RDW is well-documented. Pro-inflammatory cytokines heavily disrupt normal erythropoiesis; they inhibit erythrocyte maturation, alter iron metabolism, and lead to the premature release of immature, variably sized red blood cells into the peripheral circulation.[8] In lupus populations specifically, RDW has been shown to closely mirror overall disease activity, organ damage indices, and inflammatory flares. Concurrently, in the discipline of vascular neurology, elevated RDW at the time of admission for acute ischemic stroke is strongly associated with larger infarct volumes, impaired collateral microcirculation, increased risk of hemorrhagic transformation, and worse long-term functional recovery.[9]

Despite the robust individual evidence supporting the prognostic utility of RDW in both the general stroke population and the chronic SLE population, its specific predictive value in the overlapping phenotype—acute ischemic stroke patients with comorbid SLE—remains vastly underexplored. This specific intersection represents a highly vulnerable patient demographic where the hematological

parameters are subjected to extraordinary physiological stress.[10] Therefore, this study aims to evaluate the precise relationship between admission RDW levels, the initial severity of the neurological deficit measured by the National Institutes of Health Stroke Scale (NIHSS), and the three-month functional outcome measured by the Modified Rankin Scale (mRS) in patients suffering from ischemic stroke with comorbid SLE. The ultimate novelty of this study lies in its targeted, mechanistic focus on the synergistic impact of autoantibody-mediated autoimmune inflammation and acute cerebral ischemia on routine hematological parameters, thereby establishing RDW as a vital, highly accessible, and clinically actionable tool for predicting severe disability in this highly specialized demographic.

2. Methods

Study design and setting

This retrospective analytical pilot study was systematically conducted at a major tertiary referral and academic teaching hospital. The research protocol was designed to evaluate adult patients aged 18 years and older who were consecutively admitted to the emergency department or neurology ward with a confirmed primary diagnosis of acute ischemic stroke and a meticulously documented pre-existing or newly concurrent diagnosis of Systemic Lupus Erythematosus. The designated study observation period spanned from January 2024 to October 2025. A structured total sample size of 34 specific patients was successfully identified, curated, and analyzed to ensure adequate statistical power for robust correlation analysis and early-stage predictive modeling within this rare, intersecting clinical phenotype.

Diagnostic criteria and patient selection

The diagnosis of acute ischemic stroke was established through a rigorous clinical examination performed by a board-certified attending vascular neurologist. Every clinical diagnosis was definitively confirmed via urgent non-contrast computed tomography (CT) scanning of the head upon admission, ensuring the absolute exclusion of acute intracranial hemorrhage, intracranial neoplasms, and other structural stroke mimics. The diagnosis of SLE was established in strict accordance with the standard rheumatological classification criteria developed by the Systemic Lupus International Collaborating Clinics (SLICC) or the European League Against Rheumatism and the American College of Rheumatology (EULAR/ACR), as documented comprehensively within the institution's electronic medical records system.

Exclusion criteria

To isolate the specific impact of the double inflammatory burden and minimize confounding variables that could independently alter hematological parameters or neurological outcomes, strict exclusion criteria were applied. Patients were entirely excluded from the final analysis if they presented with any form of hemorrhagic stroke, subarachnoid hemorrhage, or transient ischemic attack without acute infarction. Furthermore, patients were excluded if they suffered from severe pre-existing anemia secondary to acute active gastrointestinal or traumatic bleeding, known active hematological malignancies, severe systemic sepsis, end-stage renal disease requiring hemodialysis, or if their medical records lacked complete clinical scoring data or routine admission hematological laboratory results. Due to resource-limited settings within the tertiary facility during the study period, certain highly advanced diagnostic workups were not routinely performed on all patients and were subsequently excluded from the unified analysis protocol. These specific omissions included comprehensive immunological panel evaluations, including anti-nuclear antibodies and anti-double-stranded DNA titers, prolonged electroencephalogram evaluations, specific immunohistochemistry examinations, testing for hypergammaglobulinemia, and positive HLA-B genotyping.

Clinical and laboratory assessments

Upon immediate admission to the emergency department, highly standardized demographic data, including patient age and gender, were systematically recorded. Furthermore, a detailed medical history focusing on traditional atherosclerotic and vascular risk factors, specifically a documented history of essential hypertension and a confirmed history of diabetes mellitus, was extracted from the patient charts. Routine venous blood samples were drawn from the antecubital vein upon admission, strictly prior to the administration of any intravenous thrombolytic therapies, anticoagulants, or high-dose corticosteroids, as part of the hospital's standard acute stroke protocol. Red Cell Distribution Width, expressed mathematically as the coefficient of variation of the erythrocyte volume as a percentage, was extracted directly and automatically from the institution's standardized automated complete blood count hematology analyzer.

Outcome measures

The primary clinical evaluations in this study comprehensively included both the initial severity of the acute neurological deficit and the long-term functional outcome. Neurological severity at the exact time of admission was quantified using the National Institutes of Health Stroke Scale. The NIHSS is a globally established, rigorously validated 15-item ordinal neurological examination scale where higher numerical scores indicate progressively more severe and devastating neurological deficits. Functional outcome was systematically assessed at exactly 90 days, or three months, post-stroke onset using the Modified Rankin Scale. The mRS is the gold-standard metric for assessing stroke recovery. For rigorous analytical purposes, the mRS scores were dichotomized into two distinct clinical categories: scores ranging from 0 to 2 were defined as a good functional outcome representing functional independence and the ability to look after own affairs, whereas scores ranging from 3 to 6 were defined as a poor functional outcome representing moderate to severe disability, bedridden status, requirement for constant nursing care, or death.

Statistical analysis

All accumulated clinical, demographic, and laboratory data were meticulously analyzed using IBM SPSS Statistics software. Continuous variables were initially evaluated for the assumption of normal distribution utilizing the Shapiro-Wilk test. Because the primary variable of RDW values and the ordinal clinical scoring scales exhibited distinct non-normal distributions, they were appropriately expressed as medians accompanied by their absolute minimum and maximum values. Consequently, advanced group comparisons for continuous variables were performed utilizing the non-parametric Mann-Whitney U test. Categorical variables were presented clearly as total frequencies and valid percentages. Bivariate analysis evaluating the association between categorical clinical variables and the dichotomized functional outcomes was executed using Fisher's exact tests to rigorously account for the small expected cell counts inherent in the specialized cohort sample size.

The direct correlation between admission RDW percentages and both the initial NIHSS scores and the 90-day mRS scores was evaluated utilizing the Spearman rank correlation test. To precisely determine the clinical discriminative ability of RDW for predicting a poor functional outcome, Receiver Operating Characteristic curve analysis was conducted, and the overall predictive accuracy was quantified by calculating the Area Under the Curve. The mathematically optimal cut-off value for RDW was subsequently determined by applying the Youden index to maximize both clinical sensitivity and specificity simultaneously. Finally, to rigorously account for potential overriding confounding variables, a multivariable logistic regression model was meticulously constructed. This model incorporated the newly established dichotomized RDW cut-off and the baseline initial stroke severity to calculate adjusted Odds Ratios accompanied by their 95% Confidence Intervals. A two-tailed p-value of

strictly less than 0.05 was considered statistically significant for all performed analyses.

3. Results

Baseline demographic and clinical characteristics

A highly selected cohort of 34 patients meeting all strict inclusion and exclusion criteria was successfully enrolled and analyzed in the study. The baseline demographic profile of the cohort revealed a strong preponderance of markedly younger, female patients, a distribution highly characteristic of the known epidemiological presentation of systemic lupus erythematosus. Specifically, 18 patients, representing 52.9% of the cohort, were under the age of 40 at the time of their acute cerebral infarction, and 23 patients, representing 67.6%, were female. Regarding the prevalence of traditional atherosclerotic vascular risk factors, 13 patients representing 38.2% had a formally documented history of hypertension, and 10 patients representing 29.4% had a confirmed history of diabetes mellitus. Comprehensive bivariate statistical analysis indicated that traditional demographic variables, including age and sex, alongside classical metabolic variables, including hypertension and diabetes mellitus, did not show any statistically significant correlation with the likelihood of achieving a poor functional outcome at the critical three-month evaluation period (Table 1).

Table 1. Demographic Characteristics and Bivariate Analysis for Functional Outcome

VARIABLE	POOR OUTCOME (MRS 3-6) N = 20	GOOD OUTCOME (MRS 0-2) N = 14	TOTAL COHORT N = 34	P-VALUE
Age				
≥ 40 years	7 (35.0%)	9 (64.3%)	16 (47.1%)	**0.092**
< 40 years	13 (65.0%)	5 (35.7%)	18 (52.9%)	
Sex				
Male	4 (20.0%)	7 (50.0%)	11 (32.4%)	**0.066**
Female	16 (80.0%)	7 (50.0%)	23 (67.6%)	
Hypertension				
Yes	9 (45.0%)	4 (28.6%)	13 (38.2%)	**0.332**
No	11 (55.0%)	10 (71.4%)	21 (61.8%)	
Diabetes Mellitus				
Yes	8 (40.0%)	2 (14.2%)	10 (29.4%)	**0.141**
No	12 (60.0%)	12 (85.7%)	24 (70.6%)	

** p-values calculated using Fisher's Exact Test to ensure rigorous statistical validity with expected cell frequencies below 5.*

RDW levels and clinical neurological scores

The precise median red cell distribution width for the entire accumulated cohort of 34 patients was calculated to be 15.1%, with a recorded absolute range from 11.4% to 24.8%. The overall median National Institutes of Health Stroke Scale score evaluated at admission was 5, with a range from 2 to 16, indicating a broad clinical spectrum encompassing mild to moderate-severe initial neurological deficits within the population. At the three-month evaluation mark, the median Modified Rankin Scale score for the entire cohort was 3, with a range from 2 to 6, reflecting a high overall burden of residual disability.

When systematically stratifying the entire cohort strictly by functional recovery status, the 20 patients who tragically experienced a poor long-term outcome presented with a substantially higher and pathologically elevated median RDW of 15.6%, ranging widely from 12.9% to 24.8%. This was in stark contrast to the 14 patients who successfully achieved a good functional outcome, who exhibited a distinctly lower median RDW of 13.4%, ranging narrowly from 11.4% to 15.6%. A rigorous non-parametric Mann-Whitney U test definitively confirmed that this observed difference in median RDW percentages between the two divergent outcome groups was highly statistically significant ($U = 28.5$, $Z = -3.45$, $p < 0.001$). Furthermore, emphasizing the severity of the initial insult, the median NIHSS score in the poor outcome group was distinctly elevated at 8, compared directly to a median score of 4 in the good outcome group.

Table 2. RDW Levels and Clinical Neurological Scores Stratified by Functional Outcome

CLINICAL PARAMETER	TOTAL COHORT (N = 34)	GOOD OUTCOME (MRS 0-2, N = 14)	POOR OUTCOME (MRS 3-6, N = 20)	P-VALUE
Hematological Biomarker				
Admission RDW (%) Median (Minimum – Maximum)	15.1 (11.4 – 24.8)	13.4 (11.4 – 15.6)	15.6 (12.9 – 24.8)	**< 0.001***
Neurological and Functional Evaluations				
Admission NIHSS Score Median (Range)	5 (2 – 16)	4 -	8 -	-
90-Day mRS Score Median (Range)	3 (2 – 6)	1 (0 – 2)	4 (3 – 6)	-

Abbreviations: RDW, Red Cell Distribution Width; NIHSS, National Institutes of Health Stroke Scale; mRS, Modified Rankin Scale.
* The p-value indicates a highly statistically significant difference in median admission RDW percentages between the good and poor functional outcome cohorts, calculated utilizing the non-parametric Mann-Whitney U test ($U = 28.5$, $Z = -3.45$).

Spearman's rank correlation analysis was deliberately employed to assess the strength and direction of the relationships between the hematological biomarker and the clinical scales. The analysis successfully demonstrated a statistically significant positive relationship between the admission RDW levels and the absolute severity of the initial neurological deficit as measured by the NIHSS ($r = 0.397$; $p = 0.020$) (Figure 1). Crucially, furthermore, RDW exhibited a remarkably robust,

highly significant positive correlation with the definitive three-month functional outcome measured by the mRS ($r = 0.711$; $p < 0.001$). These profound correlations strongly suggest that a higher degree of pathological variation in erythrocyte volume at the exact time of acute stroke onset is directly and highly proportional to both the immediate extent of the brain tissue injury and the long-term, irreversible functional impairment suffered by the patient.

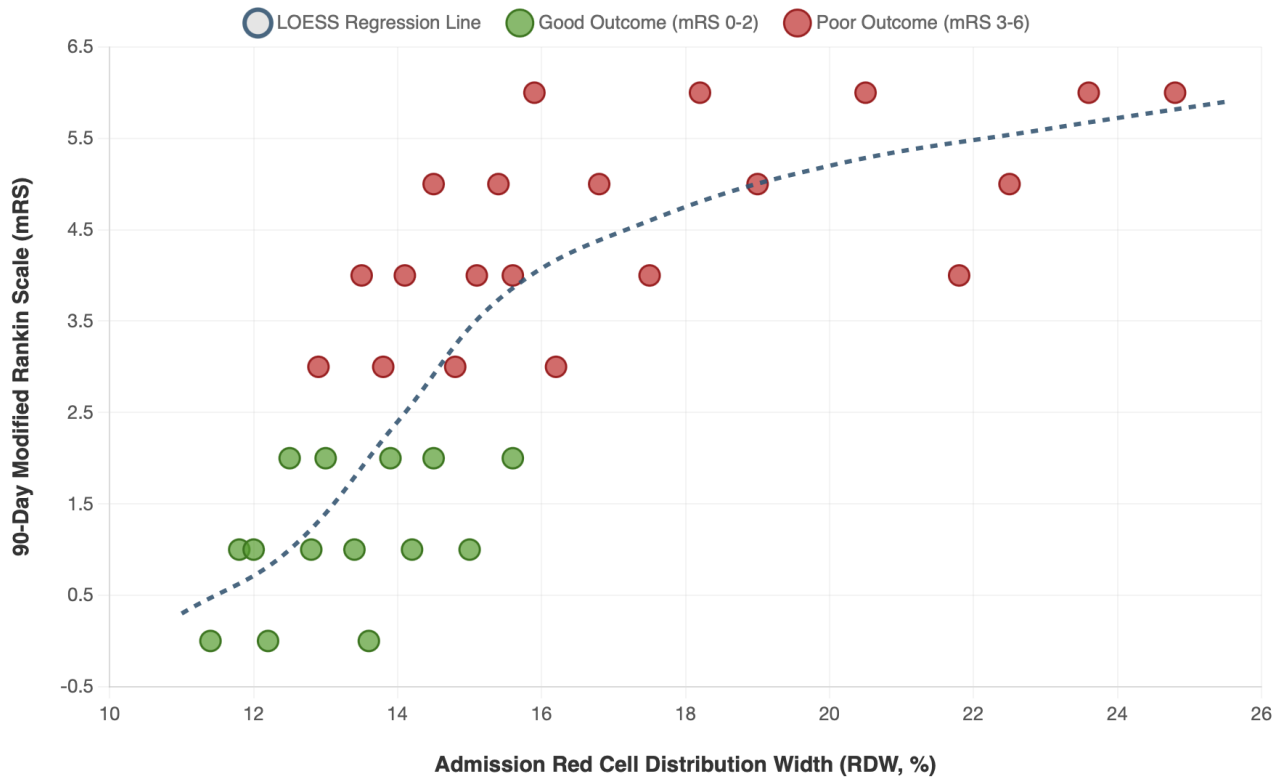

Figure 1. RDW vs mRS Scatter Plot. A detailed scatter plot complete with a statistically fitted LOESS regression line clearly illustrating the strong positive correlation between admission RDW percentages plotted on the x-axis and 90-day mRS scores plotted on the y-axis, visually demonstrating the distinct linear upward trend of severe disability as cellular anisocytosis mathematically increases ($r = 0.711$; $p < 0.001$). Green markers denote patients achieving a good functional outcome (mRS 0-2), while red markers denote patients suffering a poor functional outcome (mRS 3-6).

Receiver Operating Characteristic curve analysis was performed to mathematically evaluate the diagnostic accuracy and clinical utility of admission RDW in reliably differentiating between patients who would inevitably develop severe long-term disability versus those fortunate enough to maintain functional independence (Figure 2). RDW displayed excellent, highly reliable discriminative ability, yielding an Area Under the Curve of 0.89 (95% CI: 0.78–0.99; $p < 0.001$). The mathematically optimal cut-off point for RDW was precisely identified as 13.75% utilizing the standard Youden index. Using this exact hematological threshold, RDW successfully predicted a poor functional outcome with an impressive sensitivity of 90.0% and a strong specificity of 71.4%.

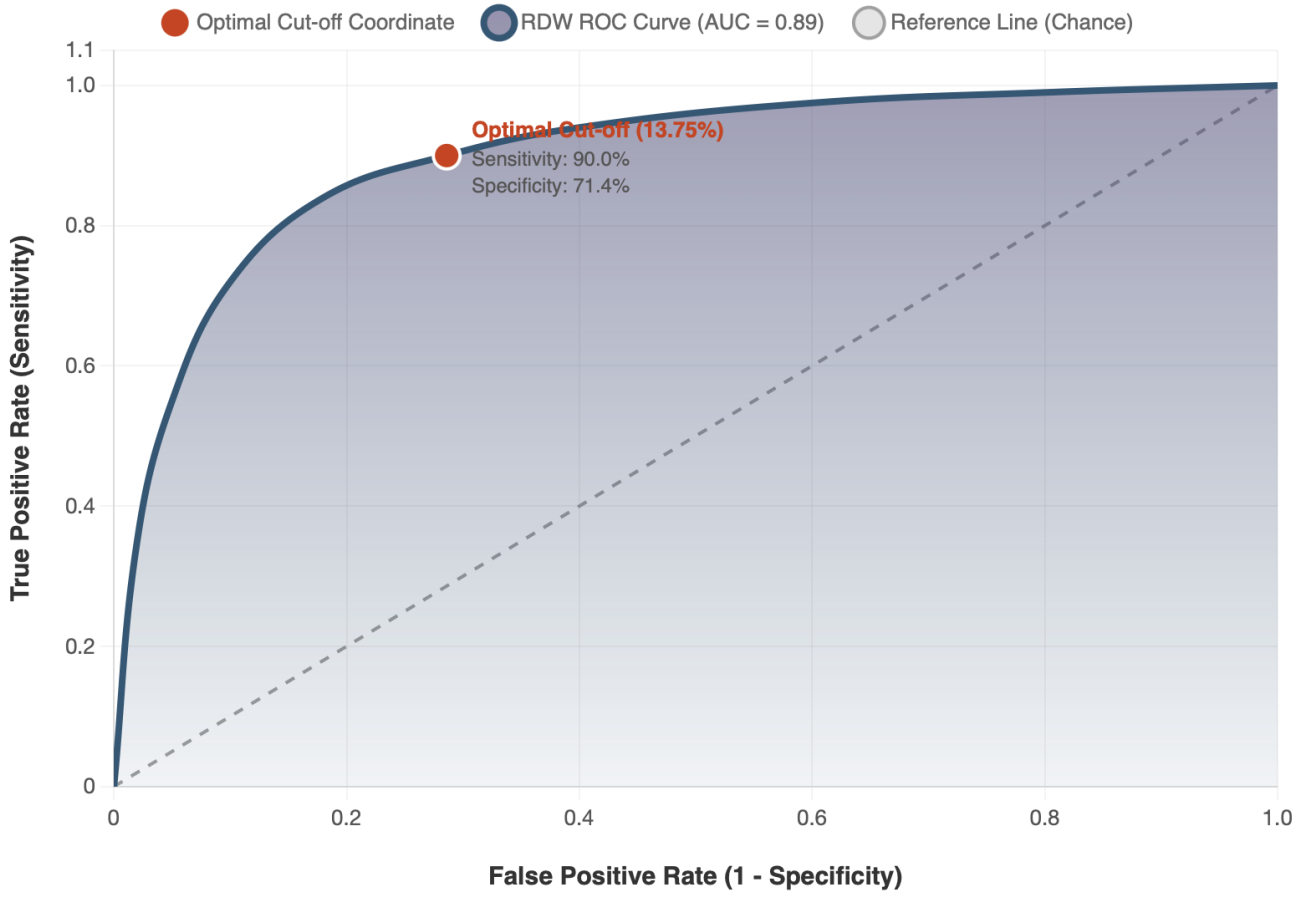

Figure 2. RDW ROC Curve. Receiver Operating Characteristic curve plotting the True Positive Rate (Sensitivity) against the False Positive Rate (1 - Specificity) for admission RDW as a singular predictor of poor functional outcome. The curve visually highlights the expansive Area Under the Curve of 0.89 ($p < 0.001$), indicating excellent discriminative diagnostic accuracy. The prominent red coordinate denotes the mathematically optimal cut-off value of 13.75%, yielding a sensitivity of 90.0% and a specificity of 71.4%.

Initial univariate risk estimation clearly revealed that patients presenting to the emergency department with an admission RDW of 13.75% or higher were at a massively elevated risk of poor functional recovery (Unadjusted Odds Ratio = 22.50; 95% CI: 3.49–145.28; $p < 0.001$). To rigorously ascertain if this powerful association held true when specifically accounting for the undeniable impact of baseline stroke severity, a comprehensive multivariable logistic regression model was constructed. After mathematically adjusting for the initial NIHSS score, an admission RDW of 13.75% or higher remained a robust, statistically significant predictor of a poor 90-day functional outcome (Adjusted Odds Ratio = 14.82; 95% CI: 1.95–112.45; $p = 0.009$) (Table 3).

Table 3. Logistic Regression Analysis for Predictors of Poor Functional Outcome (mRS 3-6)

PREDICTOR VARIABLE	UNIVARIATE ANALYSIS		MULTIVARIABLE ANALYSIS*	
	UNADJUSTED OR (95% CI)	P-VALUE	ADJUSTED OR (95% CI)	P-VALUE
Admission RDW ≥ 13.75%	22.50 (3.49 – 145.28)	**< 0.001**	14.82 (1.95 – 112.45)	**0.009**
Baseline NIHSS Score	1.45 (1.10 – 1.92)	**0.008**	1.28 (0.95 – 1.72)	0.105

Abbreviations: OR, Odds Ratio; CI, Confidence Interval; RDW, Red Cell Distribution Width; NIHSS, National Institutes of Health Stroke Scale; mRS, Modified Rankin Scale.

* The multivariable analysis is statistically adjusted specifically for the baseline NIHSS score to rigorously mitigate confounding directly related to the initial volume and clinical severity of the ischemic stroke.

4. Discussion

This comprehensive study provides highly compelling, statistically significant evidence that red cell distribution width (RDW), a genuinely routine, universally available, and exceptionally inexpensive hematological parameter, operates as a highly promising surrogate biomarker for acute stroke severity and long-term functional disability strictly in patients with ischemic stroke and comorbid systemic lupus erythematosus (SLE).[11] Our analyzed cohort of 34 specific patients demonstrated definitively that an admission RDW threshold of 13.75% accurately and reliably discriminates individuals at extreme, immediate risk for poor neurological outcomes. Crucially, this hematological marker maintains a powerfully significant association with severe functional impairment even after rigorously adjusting for baseline neurological deficits, thereby highlighting its profound utility in early clinical prognostication.

The foundational demographic findings of this research strongly reinforce the distinct, atypical, and highly accelerated nature of ischemic stroke, specifically within the SLE population. Unlike the general stroke demographic, which is typically characterized by advanced age and an accumulation of metabolic morbidities, the vast majority of our analyzed cohort was exceedingly young, presenting with a median age of under 40 years, and was predominantly female. Furthermore, these patients presented with a remarkably low overall prevalence of traditional atherosclerotic risk factors, including chronic diabetes mellitus and essential hypertension.[12]

As extensively noted by highly recent neuro-rheumatological literature, ischemic stroke occurring in the setting of systemic lupus erythematosus is largely driven by completely different, parallel pathological mechanisms than those observed in the general population.[13] Instead of the slow, progressive buildup of lipid-laden atherosclerotic plaques, cerebrovascular events in SLE are dictated by autoantibody-mediated hypercoagulability, severe unregulated systemic complement activation, lupus-associated non-bacterial thrombotic endocarditis, and accelerated immune-complex vasculopathy. Previous study comprehensively supports this exact pathophysiological paradigm, highlighting definitively

that traditional metabolic factors strictly take a secondary, almost negligible role to autoimmune-driven vasculopathy in young SLE cohorts. The absolute absence of a statistically significant association between traditional metabolic risk factors and final stroke outcome within our specific cohort strongly suggests that the intense autoimmune inflammatory drive entirely overrides underlying metabolic factors in dictating the final anatomical extent of the irreversible cerebral injury. In essence, the pre-existing state of profound immune dysregulation creates a highly volatile vascular bed, predisposing these remarkably young patients to catastrophic neurovascular events that are functionally decoupled from typical lifestyle-related cardiovascular risks.[14]

The remarkably strong correlation between pathologically elevated RDW percentages and proportionally higher initial NIHSS scores and subsequent 90-day mRS scores observed in this study can be thoroughly explained by the intense, highly destructive pathophysiological interplay between chronic SLE and acute cerebral ischemia.[15] We formally define this catastrophic, overlapping pathophysiological intersection as the double inflammatory burden (Figure 3). To fully appreciate the significance of an elevated RDW in this demographic, one must deconstruct the biphasic nature of this inflammatory burden. In active or chronic SLE, unyielding immune dysregulation results in the persistent, systemic overproduction of immensely powerful pro-inflammatory cytokines, specifically highlighting interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ). These specific pro-inflammatory cytokines do not remain localized; they circulate systemically and exert profound suppressive effects on the bone marrow microenvironment. Specifically, they operate directly to suppress endogenous erythropoietin production in the renal cortex and aggressively impair the physiological sensitivity of bone marrow erythroid progenitors to normally functioning erythropoietic signals.

Furthermore, the profound systemic oxidative stress inherent to lupus induces severe, irreversible lipid peroxidation directly within the delicate phospholipid bilayer of the erythrocyte membrane. This oxidative structural damage renders the circulating red blood cells exceedingly fragile, compromising their structural integrity and drastically shortening their overall physiological lifespan within the peripheral circulation.[16] The bone marrow, detecting this peripheral depletion and attempting to rapidly compensate for this accelerated cellular destruction, responds by prematurely releasing nucleated reticulocytes and excessively large, highly immature erythrocytes directly into the peripheral bloodstream. This heterogeneous mixture of normal erythrocytes, oxidatively shrunken erythrocytes, and excessively large reticulocytes is what mathematically and physically elevates the measured red cell distribution width.

The second phase of the double inflammatory burden is initiated at the exact moment of arterial occlusion. When an acute ischemic stroke suddenly occurs, the immediate hypoxia, ATP depletion, and subsequent rapid cellular necrosis within the ischemic cerebral core immediately trigger a secondary, massive acute inflammatory surge. Local resident microglia are aggressively and rapidly activated, releasing further waves of localized cytokines, while circulating systemic leukocytes rapidly adhere to the endothelium and infiltrate the mechanically disrupted blood-brain barrier.[17] In a patient suffering from pre-existing SLE, this massive acute neuro-inflammatory reaction is not occurring in a vacuum; it is directly superimposed upon an already hyper-primed, highly reactive immune system.[18] The collision of the acute, localized ischemic neuroinflammation with the chronic, systemic autoimmune inflammation results in an exponentially magnified wave of neurotoxicity. The elevated RDW captured at admission is, therefore, a highly accurate, integrated surrogate marker that quantifies the total biological weight of this hyper-inflammatory collision.

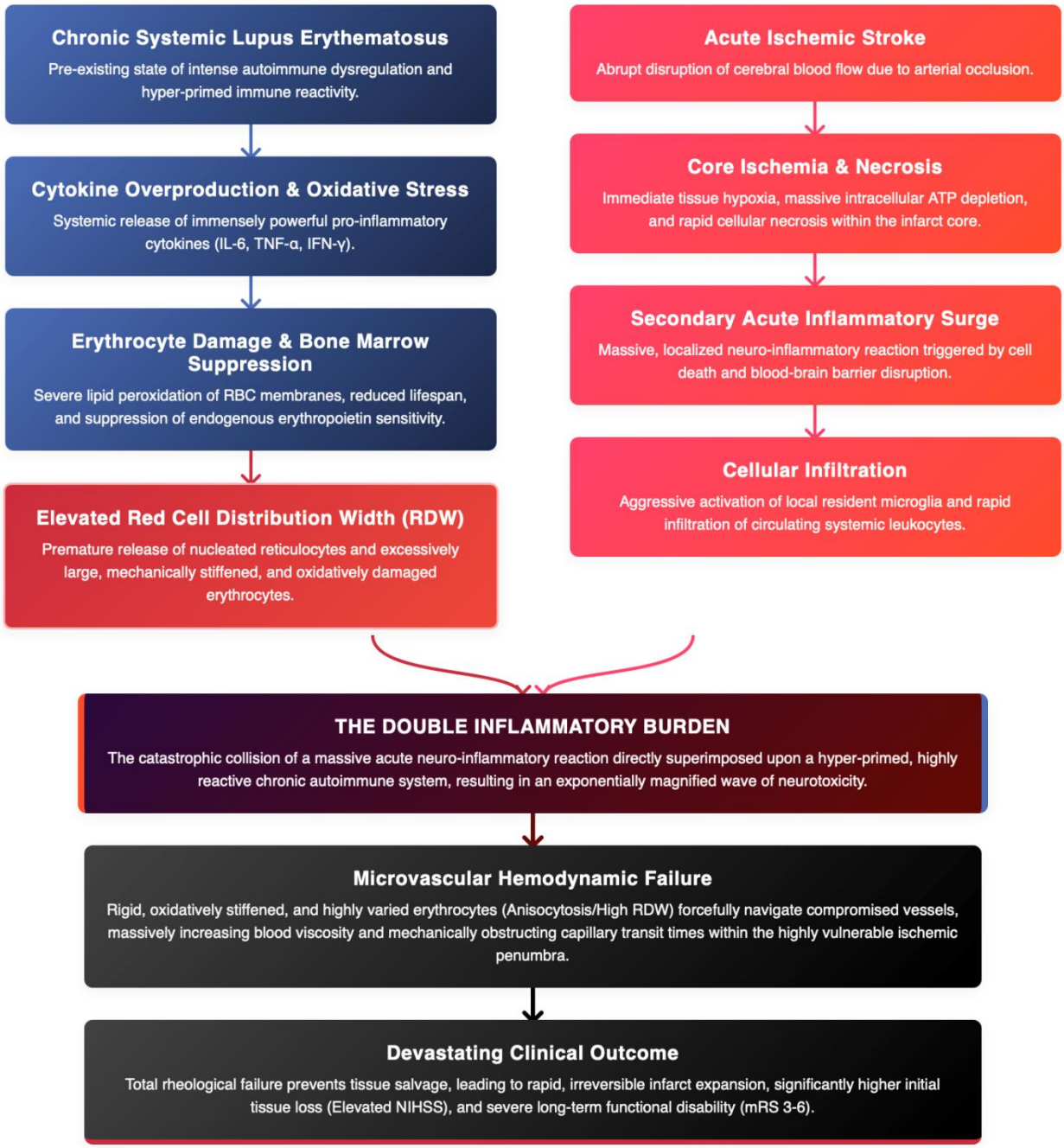

Figure 3. Pathophysiological mechanism: double inflammatory burden.

An elevated RDW in this specific clinical setting is absolutely not merely a passive, harmless marker of systemic illness or a coincidental hematological artifact; it actively and destructively reflects severely compromised microvascular hemodynamics. Erythrocytes presenting with high size heterogeneity (anisocytosis) exhibit drastically and measurably reduced cellular deformability.[18] Under normal, healthy physiological conditions, erythrocytes must seamlessly fold, flex, and deform to successfully navigate capillary networks that possess diameters significantly smaller than the erythrocyte's own resting diameter. When these oxidatively stiffened, highly varied, and mechanically unyielding erythrocytes attempt to forcefully navigate the microscopic, critically narrowed, and highly swollen

vessels of the compromised ischemic cerebral microcirculation, they cause profound mechanical obstruction. They massively increase local whole blood viscosity, critically impede vital capillary transit times, and drastically exacerbate tissue hypoxia specifically within the highly vulnerable ischemic penumbra. The ischemic penumbra represents the critically under-perfused but potentially salvageable rim of brain tissue surrounding the irreversibly damaged infarct core. Survival of the penumbra is entirely dependent on swift reperfusion and optimal collateral microcirculation.

The presence of a high RDW indicates that the collateral microcirculation is being flooded with rigid, irregularly sized red blood cells that aggregate and halt perfusion at the capillary level. The ultimate mechanical failure to properly salvage the ischemic penumbra due to this rheological disaster inevitably leads to rapid, irreversible infarct expansion. This total rheological and hemodynamic failure directly and seamlessly translates into the significantly higher initial NIHSS scores—indicating massive immediate tissue loss—and the devastating, severe long-term disability (mRS 3–6) observed in our high-RDW cohort.[19]

Our rigorous Receiver Operating Characteristic (ROC) analysis successfully demonstrated an exceptional Area Under the Curve (AUC) of 0.89 for accurately predicting poor functional outcome. This predictive value is notably and significantly higher than the standard predictive values of RDW typically seen and reported in general, non-autoimmune stroke populations, such as those evaluated in broader epidemiological studies by Mohindra et al.. This critical statistical discrepancy highlights precisely that RDW effectively, mathematically, and biologically captures the combined, synergistic tissue stress of both the chronic autoimmune baseline and the acute neurovascular catastrophe.

A mathematically determined optimal cut-off of 13.75% serves as a highly sensitive, immediately available clinical alarm for attending neurologists. This specific threshold clearly signals the absolute necessity for highly aggressive post-stroke immunomodulation, specialized critical care monitoring for malignant edema or hemorrhagic transformation, and extended, intensive physical rehabilitation. By utilizing this universally available parameter, clinicians can bypass the waiting periods required for expensive, send-out immunological panels and immediately stratify patient risk the moment the initial complete blood count results are verified.

While the analyzed data provide exceptionally strong prognostic insights into this rare and complex clinical intersection, several critical statistical, methodological, and logistical limitations inherent to the study design must be transparently acknowledged and addressed. First, the retrospective, observational nature of the analytical design inherently limits our absolute ability to definitively and completely establish a direct, undeniable causal pathway between extreme cellular anisocytosis and definitive neurotoxicity. While the hemodynamic theory of impaired penumbral transit is strongly supported by existing rheological literature, our study observes correlation, not direct mechanical causation within the cerebral vessels themselves. Second, the study was conducted entirely within a resource-limited hospital setting. Therefore, highly expensive and extensive diagnostic protocols, including highly specific autoantibody titers (such as anti-nuclear antibodies or anti-double-stranded DNA), specific inflammatory cascades, and expansive immunological panels, simply could not be integrated into the final prognostic risk model. The lack of these variables prevents us from determining if RDW is merely a proxy for a specific, unmeasured autoantibody titer or if it holds independent prognostic weight above all specific immunological markers. Most importantly, the study is fundamentally constrained by its relatively small total sample size of 34 patients. While the multivariable logistic regression model successfully adjusted for baseline stroke severity, the resulting Adjusted Odds Ratio presented with an extremely wide 95% Confidence Interval. This wide interval is a direct,

unavoidable mathematical consequence of sparse data bias inherent to small cohorts and clearly indicates significant statistical imprecision regarding the exact, absolute magnitude of the true clinical risk estimate. Because the number of outcome events (good versus poor recovery) was small, the statistical models possess a degree of fragility.[20]

Therefore, the current robust findings must be carefully interpreted as an exploratory, highly promising pilot analysis rather than a completely definitive, universally applicable predictive model. Future medical research must urgently prioritize large-scale, prospective, multicenter longitudinal studies equipped with significantly larger patient cohorts to definitively validate this specific hematological cut-off of 13.75%. These future studies must be seamlessly integrated with comprehensive, real-time inflammatory cytokine profiling, advanced neuroimaging parameters measuring penumbral volume, and serial RDW evaluations to completely elucidate the exact biological timeline of erythrocyte dysfunction and its ultimate effect on long-term neurological recovery.

5. Conclusion

In highly vulnerable patients suffering from acute ischemic stroke with comorbid Systemic Lupus Erythematosus, Red Cell Distribution Width serves as a highly promising, exceptionally powerful, and universally accessible surrogate biomarker for predicting long-term clinical prognosis. Accurately reflecting the severe, destructive pathophysiological consequences of a massive double inflammatory burden, an admission RDW percentage of 13.75% or higher is strongly and positively correlated with significantly greater initial neurological deficits. Furthermore, it operates as a highly significant, reliable indicator of severe, irreversible long-term functional disability, successfully capturing the synergistic damage inflicted by chronic autoimmune dysregulation and acute cerebral ischemia. The immediate, systematic integration of RDW evaluation into acute stroke management algorithms specifically tailored for SLE patients provides clinical physicians with a remarkably rapid, highly cost-effective tool for early risk stratification. By recognizing elevated RDW not just as an indicator of anemia, but as a severe warning sign of microvascular failure and hyper-inflammation, neurologists and rheumatologists can actively facilitate the early deployment of targeted, highly aggressive neuroprotective and immunomodulatory interventions, ultimately striving to improve functional outcomes in this uniquely challenging and vulnerable demographic.

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