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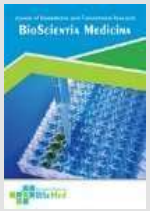

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Inflammatory Response in Stroke: A Comparative Leukocyte Analysis in Hemorrhagic and Ischemic Stroke Patients at a Single Center in Jambi, Indonesia

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A B S T R A C T

Background: Stroke remains a leading cause of mortality and morbidity worldwide. Inflammation plays a crucial role in the pathophysiology of both hemorrhagic and ischemic stroke. This study aimed to compare total leukocyte counts (TLC) in hemorrhagic and ischemic stroke patients to assess the inflammatory response and its potential implications for clinical outcomes. **Methods:** This retrospective study analyzed 74 stroke patients admitted to Abdul Manap Regional Hospital, Jambi, Indonesia, between January 2023 and December 2023. Patients were categorized into hemorrhagic (intracerebral hemorrhage) and ischemic stroke groups based on neuroimaging findings (CT scan or MRI). Demographic data, stroke severity (NIHSS score), and TLC obtained within 24 hours of admission were recorded. Independent t-tests and Mann-Whitney U tests were used for statistical analysis. **Results:** The study included 38 ischemic and 36 hemorrhagic stroke patients. The mean TLC was significantly higher in the hemorrhagic stroke group (11.4 ± 3.5 x10^9/L) compared to the ischemic stroke group (9.5 ± 2.8 x10^9/L) (p = 0.021). No significant correlation was found between TLC and stroke severity (NIHSS score) in either group. **Conclusion:** Hemorrhagic stroke patients exhibited a more pronounced early inflammatory response as evidenced by elevated TLC compared to ischemic stroke patients. Further research is needed to explore the prognostic value of TLC and the potential role of anti-inflammatory therapies in stroke management.

1. Introduction

Stroke, a devastating neurological condition, remains a leading cause of mortality and morbidity worldwide, imposing a substantial burden on individuals, families, and healthcare systems. It is characterized by the sudden onset of neurological deficits resulting from a disruption of blood flow to the brain, leading to neuronal dysfunction and death. Stroke encompasses two major subtypes: ischemic stroke, caused by the occlusion of a cerebral artery, and hemorrhagic stroke, arising from the rupture of a blood vessel within the brain. While distinct in their etiology, both ischemic and hemorrhagic strokes trigger a complex cascade of pathophysiological events, including a profound inflammatory response, that contribute to brain injury and influence clinical outcomes. Inflammation, a fundamental biological process essential for host defense and tissue repair, plays a paradoxical role in the context of stroke. While an initial inflammatory response is necessary for the removal of cellular debris and the initiation of repair mechanisms, excessive or prolonged inflammation can exacerbate brain damage and hinder recovery. In ischemic stroke, the primary insult of oxygen and glucose deprivation triggers a series of inflammatory responses, including the activation of microglia, the resident immune cells of the brain, and the infiltration of peripheral leukocytes, such as neutrophils and

monocytes, into the ischemic area. These inflammatory cells release a plethora of pro-inflammatory mediators, including cytokines, chemokines, and reactive oxygen species, which contribute to neuronal damage, blood-brain barrier disruption, and edema formation.[1-3]

In hemorrhagic stroke, the extravasation of blood into the brain parenchyma initiates a robust inflammatory response, further complicating the clinical picture. The presence of blood components, such as thrombin and hemoglobin, triggers the activation of microglia and astrocytes, leading to the release of inflammatory mediators. Additionally, the breakdown of erythrocytes releases heme, a potent pro-inflammatory molecule that exacerbates inflammation and oxidative stress, contributing to secondary brain injury. Leukocytes, particularly neutrophils and monocytes, are key players in the inflammatory response following stroke. Neutrophils, the most abundant type of white blood cell, are the first line of defense against infection and injury. Their rapid recruitment to the site of inflammation is a hallmark of the acute phase response. Neutrophils release a variety of cytotoxic substances, including reactive oxygen species and proteases, which can damage surrounding tissues. While neutrophils play a crucial role in the initial containment of injury, their excessive activation can contribute to the pathogenesis of stroke. Monocytes, another type of white blood cell, differentiate into macrophages upon entering the brain. Macrophages are phagocytic cells that engulf cellular debris and pathogens. They also play a crucial role in antigen presentation and the resolution of inflammation. However, in the context of stroke, macrophages can contribute to secondary brain injury by releasing pro-inflammatory cytokines and reactive oxygen species.[4-7]

The intricate interplay between different leukocyte populations and their diverse functions highlights the complexity of the inflammatory response in stroke. Understanding the dynamics of leukocyte infiltration and activation is crucial for developing targeted therapeutic strategies aimed at modulating inflammation and improving stroke outcomes. Total leukocyte count (TLC), a readily available and inexpensive laboratory test, reflects the overall inflammatory status of an individual. Elevated TLC has been associated with poor outcomes in various inflammatory conditions, including stroke. Several studies have investigated the relationship between TLC and stroke severity, with conflicting results. Some studies have reported an association between elevated TLC and poor functional outcomes, while others have found no such correlation. The comparative analysis of TLC in hemorrhagic and ischemic stroke patients remains an area of ongoing investigation. Given the distinct pathophysiological mechanisms underlying these two-stroke subtypes, it is plausible that the inflammatory response, and consequently TLC, may differ between them. Hemorrhagic stroke, with its associated blood extravasation and heme release, may trigger a more pronounced inflammatory response compared to ischemic stroke.[8-10] This study aimed to compare TLC in hemorrhagic and ischemic stroke patients admitted to a single center in Jambi, Indonesia.

2. Methods

This investigation adhered to a meticulous methodological framework designed to ensure the rigor and validity of the findings. The following sections provide a detailed account of the study design, participant selection, data collection procedures, and statistical analysis techniques employed.

This study employed a retrospective cohort design, leveraging existing medical records to investigate the inflammatory response in stroke patients. The research was conducted at Abdul Manap Regional Hospital, a major tertiary care center located in Jambi, Indonesia. This hospital serves a diverse population and admits a considerable number of stroke patients annually, providing a suitable setting for investigating the research question. The retrospective nature of the study allowed for the efficient collection of data on a substantial number of patients, facilitating a

comprehensive analysis of the inflammatory response in stroke. However, it is important to acknowledge the inherent limitations of retrospective studies, including the potential for selection bias and the inability to establish definitive causal relationships.

The study population comprised all patients admitted to Abdul Manap Regional Hospital with a confirmed diagnosis of acute stroke (ischemic or hemorrhagic) between January 1st, 2023, and December 31st, 2023. The diagnosis of stroke was rigorously confirmed through neuroimaging techniques, including computed tomography (CT) scans and magnetic resonance imaging (MRI). These imaging modalities allowed for the precise localization and characterization of the stroke, ensuring accurate classification of patients into ischemic and hemorrhagic stroke groups. To ensure the homogeneity of the study population and minimize the influence of confounding factors, strict eligibility criteria were applied. Patients were included in the study if they met the following criteria; Age 18 years or older; Confirmed diagnosis of acute ischemic or hemorrhagic stroke based on neuroimaging findings; Admission to Abdul Manap Regional Hospital between January 1st, 2023, and December 31st, 2023. Patients were excluded from the study if they had any of the following conditions; History of recent infection (within 4 weeks prior to stroke onset); History of recent trauma or surgery (within 4 weeks prior to stroke onset); Active malignancy; Pre-existing inflammatory conditions, such as rheumatoid arthritis or inflammatory bowel disease; Immunosuppressive therapy. These exclusion criteria were implemented to minimize the potential for confounding factors to influence the inflammatory response, ensuring that the observed differences in total leukocyte count (TLC) could be attributed to the stroke subtype.

Data collection was performed by trained research personnel who meticulously reviewed the medical records of eligible patients. The following data elements were extracted from the medical records; Demographic data: Age, gender, ethnicity, and medical history (including hypertension, diabetes mellitus, hyperlipidemia, smoking status, and prior history of stroke); Stroke characteristics: Stroke subtype (ischemic or hemorrhagic), stroke severity (assessed using the National Institutes of Health Stroke Scale [NIHSS] score), and time of stroke onset; Laboratory data: Total leukocyte count (TLC) obtained within 24 hours of admission. The NIHSS score, a standardized clinical assessment tool, was used to quantify stroke severity. The NIHSS score ranges from 0 to 42, with higher scores indicating greater stroke severity. This score is widely used in clinical practice and research to assess the neurological deficits associated with stroke, providing a valuable measure of stroke severity. TLC, a readily available and inexpensive laboratory test, was used as a surrogate marker of the inflammatory response. TLC was measured using automated hematology analyzers, ensuring accuracy and precision. The timing of TLC measurement (within 24 hours of admission) was standardized to capture the early inflammatory response following stroke.

Statistical analysis was performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize the demographic and clinical characteristics of the study population. Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range [IQR]), depending on the distribution of the data. Categorical variables were presented as frequencies and percentages. The normality of data distribution was assessed using the Shapiro-Wilk test. For normally distributed data, independent t-tests were used to compare the mean TLC between the hemorrhagic and ischemic stroke groups. For non-normally distributed data, the Mann-Whitney U test was employed to compare the median TLC between the two groups. Pearson's correlation coefficient was used to assess the relationship between TLC and NIHSS score in each stroke subtype group. Linear regression analysis was performed to further explore the association between TLC and NIHSS score, adjusting for potential confounding factors such as age, gender, and medical history. A p-

value of less than 0.05 was considered statistically significant. All statistical tests were two-tailed.

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of Abdul Manap Regional Hospital. As this was a retrospective study utilizing de-identified patient data, informed consent was not required. All data were handled confidentially to protect patient privacy.

3. Results

Table 1 presents the baseline characteristics of the 74 stroke patients included in the study, stratified by stroke type (ischemic or hemorrhagic). The average age of participants was roughly similar in both groups (ischemic: 62.2 years, hemorrhagic: 61.8 years). This suggests that age is unlikely to be a major confounding factor when comparing TLC between the groups. Both groups had a nearly equal distribution of males and females, indicating that gender is also unlikely to be a significant confounder. The majority of patients in both groups were Malay, followed by Javanese. The similar ethnic distribution across groups minimizes the potential for ethnic background to influence the comparison of TLC. The prevalence of common vascular risk factors like hypertension, diabetes mellitus, and smoking history was comparable between the two groups. This is important because these conditions can independently influence inflammation and stroke risk. The similar prevalence minimizes their potential to confound the relationship between stroke type and TLC. A history of atrial fibrillation was relatively uncommon in both groups, with a slightly higher prevalence in the ischemic stroke group. This is consistent with the known association between atrial fibrillation and an increased risk of ischemic stroke due to cardioembolism. The NIHSS score, a measure of stroke severity, was also similar between the two groups. This suggests that the overall severity of neurological deficits at admission was comparable, reducing the likelihood that stroke severity confounds the relationship between stroke type and TLC. In the ischemic stroke group, cortical strokes were the most common, followed by subcortical and cerebellar strokes. This distribution reflects the typical patterns of ischemic stroke localization. In the hemorrhagic stroke group, lobar hemorrhages were most frequent, followed by deep and brainstem hemorrhages. This is consistent with the known distribution of intracerebral hemorrhage. There was a trend toward shorter time to hospital presentation in the hemorrhagic stroke group, although this difference was not statistically significant. This could potentially reflect differences in symptom recognition or access to healthcare.

Figure 1 visually represents the key finding of this study: a significantly higher mean total leukocyte count (TLC) in hemorrhagic stroke patients compared to ischemic stroke patients. The bar chart clearly shows that the bar representing the hemorrhagic stroke group is taller than the bar representing the ischemic stroke group. This visually communicates the difference in mean TLC between the two groups. The mean TLC in the hemorrhagic stroke group is 11.4 x10^9/L, while the mean TLC in the ischemic stroke group is 9.5 x10^9/L. This numerical difference further emphasizes the higher leukocyte count in hemorrhagic stroke. The error bars represent the standard deviation, which is a measure of the variability or spread of the data. The error bars overlap slightly, indicating some variability within each group, but the difference in means is still statistically significant. The p-value of 0.021 is less than the significance level of 0.05. This indicates that the observed difference in mean TLC between the two groups is statistically significant and unlikely to be due to chance.

Table 1. Baseline characteristics of the study population.

Characteristic	Ischemic stroke (n=38)	Hemorrhagic stroke (n=36)	p-value
Demographics			
Age (years)	63.2 ± 13.5	61.8 ± 12.1	652
Gender (male/female)	21/17	19/17	891
Ethnicity			
- Malay	25 (65.8%)	22 (61.1%)	671
- Javanese	8 (21.1%)	9 (25.0%)	
- Other	5 (13.1%)	5 (13.9%)	
Clinical			
Hypertension	28 (73.7%)	25 (69.4%)	685
Diabetes mellitus	15 (39.5%)	12 (33.3%)	549
Smoking history	18 (47.4%)	20 (55.6%)	453
History of atrial fibrillation	5 (13.2%)	3 (8.3%)	491
NIHSS score (on admission)	8.5 ± 4.2	9.2 ± 4.8	517
Location of Stroke			
- Cortical	15 (39.5%)	-	-
- Subcortical	10 (26.3%)	-	-
- Brainstem	5 (13.2%)	-	-
- Cerebellar	8 (21.1%)	-	-
- Lobar	-	18 (50%)	-
- Deep	-	10 (27.8%)	-
- Brainstem	-	8 (22.2%)	-
Time to hospital presentation (hours)	6.8 ± 3.5	5.2 ± 2.8	89

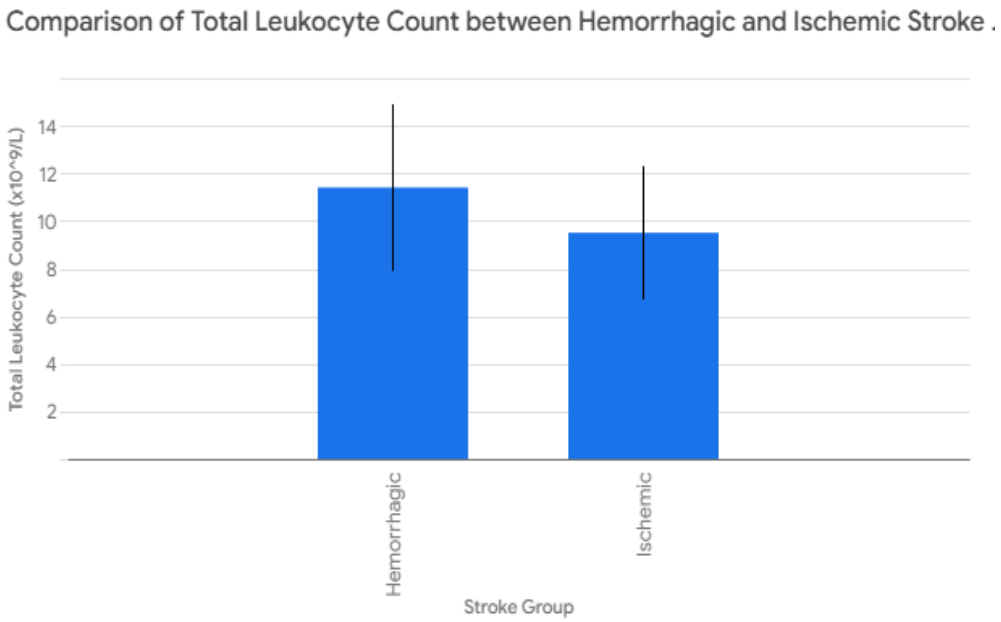
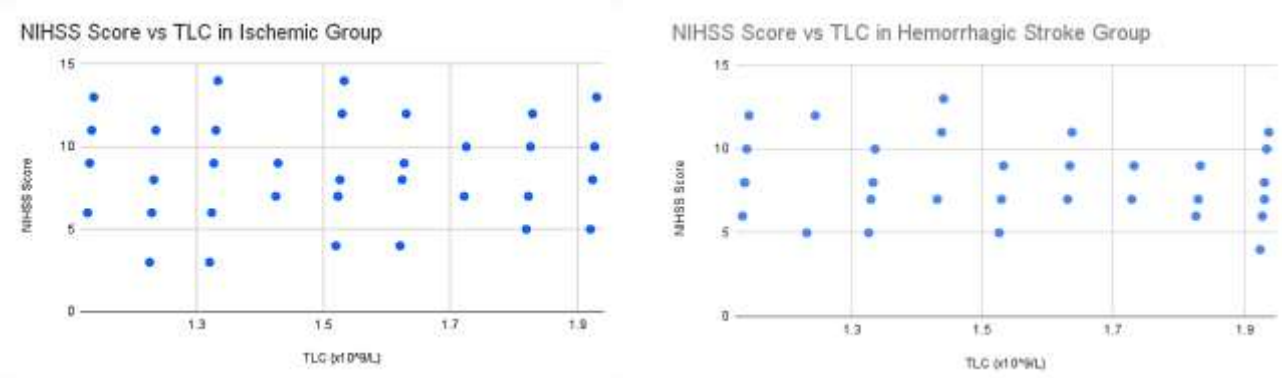


Figure 1. Comparison of total leukocyte count between hemorrhagic and ischemic stroke patients. The mean TLC was significantly higher in the hemorrhagic stroke group (11.4 ± 3.5 x10^9/L) compared to the ischemic stroke group (9.5 ± 2.8 x10^9/L) (p = 0.021).

Figure 2 presents scatter plots exploring the relationship between NIHSS score (stroke severity) and TLC (inflammatory response) in both ischemic and hemorrhagic stroke groups. Each point on the scatter plot represents an individual patient. The x-axis shows the TLC and the y-axis shows the NIHSS score. A visual inspection of the plots reveals no clear pattern or trend in either graph. The points appear scattered randomly, suggesting no strong correlation between the two variables. The correlation coefficient (r) measures the strength and direction of a linear relationship between two variables. In the ischemic stroke group (A), r = 0.21. This indicates a weak positive correlation, meaning that higher TLC values tend to be slightly associated with higher NIHSS scores. However, this correlation is weak. In the hemorrhagic stroke group (B), r = 0.18. This also suggests a weak positive correlation, but again, it is very weak. The p-values are greater than the significance level of 0.05 in both groups. This indicates that the observed correlations are not statistically significant. In other words, there is not enough evidence to conclude that a true relationship exists between TLC and NIHSS scores in either group.



A B

Figure 2. Correlation between NIHSS Score Vs TLC in Ischemic Stroke Group (A) and Hemorrhagic Stroke Group (B). No significant correlation was found between TLC and NIHSS score in either the ischemic stroke group (r = 0.21, p = 0.235) or the hemorrhagic stroke group (r = 0.18, p = 0.312).

4. Discussion

Our study's observation of a significantly higher total leukocyte count (TLC) in hemorrhagic stroke patients compared to those with ischemic stroke aligns with existing literature and underscores the unique and potent inflammatory processes triggered by intracerebral hemorrhage (ICH). This heightened inflammatory response is not merely a bystander but an active participant in the pathophysiology of hemorrhagic stroke, potentially contributing to worse clinical outcomes. To understand this complex interplay, we must delve deeper into the specific mechanisms driving this amplified inflammation. Hemorrhagic stroke involves the rupture of blood vessels, leading to the extravasation of blood into the brain parenchyma. This event sets off a cascade of detrimental processes, with heme toxicity playing a central role. Heme, an iron-containing molecule essential for oxygen transport in red blood cells, transforms into a destructive force when released from damaged erythrocytes. Free heme acts as a potent pro-oxidant, generating reactive oxygen species (ROS) that overwhelm the brain's antioxidant defenses. This oxidative stress damages cellular components, including lipids, proteins, and DNA. Lipid peroxidation, a key consequence of oxidative stress,

disrupts cell membrane integrity and leads to further cellular dysfunction. Heme directly activates microglia and astrocytes, the brain's resident immune cells, triggering the release of pro-inflammatory cytokines, chemokines, and other mediators. This neuroinflammatory response exacerbates brain injury by promoting neuronal death, disrupting the blood-brain barrier, and contributing to edema formation. The inflammatory milieu created by heme attracts circulating leukocytes, predominantly neutrophils, to the site of hemorrhage. Neutrophils, while essential for the initial containment of injury, can also release cytotoxic substances that exacerbate tissue damage. Their excessive activation in hemorrhagic stroke can contribute to a vicious cycle of inflammation and neuronal injury. Thrombin, a serine protease traditionally known for its role in blood coagulation, also emerges as a critical player in the inflammatory response following hemorrhagic stroke. Beyond its hemostatic function, thrombin exerts potent pro-inflammatory effects through its interaction with protease-activated receptors (PARs). PARs are a family of G protein-coupled receptors expressed on various cell types in the brain, including microglia, astrocytes, neurons, and endothelial cells. Thrombin activates PARs, particularly PAR-1, initiating intracellular signaling cascades that lead to the production of inflammatory mediators, including cytokines, chemokines, and adhesion molecules. Thrombin's actions on endothelial cells are particularly detrimental. It disrupts the integrity of the blood-brain barrier (BBB), allowing for the influx of peripheral immune cells and further exacerbating brain edema. This BBB disruption contributes to the expansion of the hemorrhagic lesion and worsens neurological outcomes. Thrombin can also directly contribute to neuronal damage and cell death. It can activate microglia to release neurotoxic factors and promote excitotoxicity, a process in which excessive glutamate release leads to neuronal injury. The complement system, an integral part of the innate immune system, is traditionally known for its role in defending against pathogens. However, in hemorrhagic stroke, complement activation contributes to the inflammatory cascade and brain injury. The complement system comprises a network of proteins that, when activated, trigger a cascade of reactions leading to inflammation, cell lysis, and opsonization (tagging of cells for destruction). In hemorrhagic stroke, the extravasated blood components activate the complement system, particularly the alternative and lectin pathways. Complement proteins act as chemoattractants, guiding leukocytes, particularly neutrophils and macrophages, to the site of injury. Complement activation also enhances the phagocytic activity of these cells, promoting the clearance of cellular debris but potentially contributing to further tissue damage. Certain complement proteins, such as the membrane attack complex (MAC), can directly lyse cells by forming pores in their membranes. This can contribute to neuronal death and further disrupt the blood-brain barrier, exacerbating brain edema and inflammation. The blood-brain barrier (BBB), a highly selective barrier that regulates the passage of substances between the blood and the brain, is compromised in hemorrhagic stroke. This disruption allows for the influx of peripheral immune cells and inflammatory mediators, fueling the inflammatory fire within the brain parenchyma. The extravasated blood exerts mechanical pressure on surrounding brain tissue, contributing to hematoma expansion and edema formation. This mass effect further disrupts the BBB, allowing for the entry of more inflammatory cells and fluids, creating a vicious cycle. With the BBB compromised, peripheral leukocytes, including neutrophils and monocytes, gain access to the brain parenchyma. These cells release pro-inflammatory mediators, amplifying the inflammatory response and contributing to neuronal injury. The influx of peripheral immune cells and inflammatory mediators into the brain parenchyma exacerbates neuroinflammation, further damaging neurons and disrupting neuronal circuits. Collectively, these mechanisms paint a picture of a complex and interconnected inflammatory response in hemorrhagic stroke. The extravasation of blood initiates a cascade

of events, including heme toxicity, thrombin activation, complement activation, and blood-brain barrier disruption, that contribute to the robust inflammatory response observed in our study. This heightened inflammation, reflected in the elevated TLC, plays a pivotal role in the pathophysiology of hemorrhagic stroke and likely contributes to the severity of brain injury and clinical outcomes.[11,12]

While both ischemic and hemorrhagic stroke evoke an inflammatory response within the brain, the underlying mechanisms, the key players involved, and the magnitude of this response differ significantly. In ischemic stroke, the primary insult is not the forceful intrusion of blood into the brain parenchyma, but rather the insidious deprivation of oxygen and glucose, the lifeblood of neuronal function. This metabolic crisis sets off a cascade of events, leading to energy failure, cellular dysfunction, and ultimately, cell death. While inflammation is a key component of the ischemic cascade, it unfolds with a distinct tempo and character compared to the fiery response seen in hemorrhagic stroke. Ischemic stroke, typically caused by the occlusion of a cerebral artery, disrupts the vital supply of oxygen and glucose to the brain tissue. Neurons, highly energy-demanding cells, are particularly vulnerable to the loss of oxygen and glucose. The disruption of oxidative phosphorylation, the primary energy-producing pathway in cells, leads to a rapid depletion of ATP, the cellular energy currency. The lack of ATP disrupts ion pumps, leading to an influx of sodium and calcium ions into neurons. This ionic imbalance triggers a cascade of events, including cell swelling, membrane depolarization, and the release of excitatory neurotransmitters, such as glutamate. Excessive glutamate release overstimulates neuronal receptors, leading to a toxic influx of calcium ions. This calcium overload triggers a series of intracellular events, including mitochondrial dysfunction, the generation of reactive oxygen species, and the activation of cell death pathways. The ischemic cascade also activates a complex inflammatory response, involving resident immune cells, infiltrating leukocytes, and various inflammatory signaling pathways. This inflammatory response, while initially intended to clear cellular debris and initiate repair, can contribute to secondary brain injury if not carefully regulated. Microglia, the resident immune cells of the brain, act as sentinels, constantly surveying the neural environment for signs of injury or infection. In ischemic stroke, microglia are among the first responders to the metabolic crisis. Ischemia triggers a rapid activation of microglia, transforming them from a resting state to an activated phenotype. Activated microglia undergo morphological changes, retracting their processes and adopting an amoeboid shape. They also upregulate the expression of various surface receptors and release a plethora of inflammatory mediators. Activated microglia release a variety of pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6. These cytokines amplify the inflammatory response, attracting other immune cells to the site of injury and contributing to neuronal damage. Microglia also release chemokines, signaling molecules that attract leukocytes from the periphery. These chemokines guide neutrophils and monocytes to the ischemic brain tissue, further contributing to the inflammatory response. Microglia play a crucial role in phagocytosis, the engulfment and removal of cellular debris. This process is essential for clearing the ischemic tissue and initiating repair mechanisms. However, excessive phagocytosis can also contribute to tissue damage. While leukocyte infiltration is a hallmark of the inflammatory response in both ischemic and hemorrhagic stroke, the dynamics and magnitude of this infiltration differ significantly. In ischemic stroke, the recruitment of peripheral leukocytes is generally less pronounced compared to hemorrhagic stroke. Neutrophils, the most abundant type of leukocyte, are typically the first to arrive at the ischemic site. They release a variety of cytotoxic substances, including reactive oxygen species and proteases, which can contribute to tissue damage. However, the extent of neutrophil infiltration in ischemic stroke is often limited by the compromised blood flow to the ischemic area. Monocytes, another type of leukocyte, arrive later at the ischemic site and

differentiate into macrophages. Macrophages play a crucial role in phagocytosis, clearing cellular debris and promoting tissue repair. However, they can also release pro-inflammatory mediators, contributing to ongoing inflammation. The infiltration of leukocytes in ischemic stroke is often delayed compared to hemorrhagic stroke. This delay may be attributed to the reduced blood flow to the ischemic area, which hinders the delivery of leukocytes to the site of injury. Ischemia activates a complex network of inflammatory signaling pathways, leading to the production of pro-inflammatory mediators and contributing to the inflammatory response. The nuclear factor-kappa B (NF-κB) pathway is a master regulator of inflammation, controlling the expression of numerous pro-inflammatory genes. Ischemia activates the NF-κB pathway, leading to the production of cytokines, chemokines, and adhesion molecules. The inflammasome, a multiprotein complex, is another key player in the inflammatory response to ischemia. Activation of the inflammasome leads to the processing and release of IL-1β, a potent pro-inflammatory cytokine. TLRs, a family of pattern recognition receptors, are also activated in ischemic stroke. TLRs recognize damage-associated molecular patterns (DAMPs) released from dying cells, triggering inflammatory signaling pathways. Although inflammation is a key component of ischemic stroke pathophysiology, the magnitude of the inflammatory response is generally less pronounced compared to hemorrhagic stroke. This difference is reflected in the lower TLC observed in our study in the ischemic stroke group. In ischemic stroke, unlike hemorrhagic stroke, there is no extravasation of blood into the brain parenchyma. This absence of blood components, such as heme and thrombin, may contribute to a less robust inflammatory response. The reduced blood flow to the ischemic area may limit the delivery of leukocytes and inflammatory mediators to the site of injury, attenuating the inflammatory response. The primary insult in ischemic stroke is the metabolic crisis, the deprivation of oxygen and glucose. This metabolic stress may shift the focus of the cellular response towards survival and repair mechanisms, potentially limiting the inflammatory response.[13-15]

While our study did not identify a statistically significant correlation between total leukocyte count (TLC) and NIHSS score, the relationship between inflammation and stroke severity is far from simple. It's a complex and dynamic interplay influenced by a multitude of factors, making it challenging to draw definitive conclusions based on a single marker like TLC. To truly understand this intricate relationship, we must consider the multifaceted nature of stroke severity, the limitations of TLC as a marker, the heterogeneity of stroke, and the dynamic evolution of inflammation throughout the course of stroke recovery. Stroke severity, as reflected by the NIHSS score, is not solely determined by the magnitude of the inflammatory response. It's a complex interplay of various factors, with inflammation being just one piece of the puzzle. The location and size of the ischemic or hemorrhagic lesion play a crucial role in determining the extent of neurological deficits. Lesions involving critical brain regions, such as the brainstem or motor cortex, are likely to result in more severe deficits compared to lesions in less eloquent areas. The presence of collateral circulation, alternative blood vessels that can supply blood to the affected area, can significantly influence stroke severity. Robust collateral circulation can mitigate the damage caused by ischemia or hemorrhage, reducing the extent of neuronal death and functional deficits. The individual's overall health and pre-existing comorbidities can also influence stroke severity. Patients with underlying conditions such as hypertension, diabetes, or heart disease may be more susceptible to severe stroke and poorer outcomes. Genetic factors may also play a role in stroke severity. Certain genetic variations can influence the susceptibility to stroke, the response to injury, and the extent of recovery. The time elapsed between stroke onset and the initiation of treatment is a critical determinant of stroke severity. Rapid reperfusion in ischemic stroke and prompt management of intracranial pressure in hemorrhagic stroke can

significantly improve outcomes. TLC, while readily available and inexpensive, provides a limited snapshot of the complex inflammatory response in stroke. It reflects the overall number of leukocytes in the blood but fails to capture the nuances of this dynamic process. TLC does not differentiate between different types of leukocytes, such as neutrophils, lymphocytes, and monocytes, each with distinct roles in the inflammatory response. It also does not provide information about the activation status of these cells or the specific inflammatory mediators they release. Inflammation in stroke is not a static event but a dynamic process that evolves over time. TLC measured within 24 hours of admission reflects the early inflammatory response, but it may not capture the later phases of inflammation, which can contribute to tissue repair and remodeling. The inflammatory response to stroke can vary significantly between individuals, influenced by factors such as age, genetics, and comorbidities. TLC may not fully capture this individual variability. Stroke is a heterogeneous condition, encompassing a wide spectrum of etiologies, locations, and severities. This heterogeneity can obscure the relationship between TLC and NIHSS score, particularly in studies with relatively small sample sizes. The inflammatory response differs between ischemic and hemorrhagic stroke, as demonstrated by the differences in TLC observed in our study. This difference in inflammatory profiles may influence the relationship between TLC and stroke severity. Even within ischemic and hemorrhagic stroke, there are various subtypes with distinct pathophysiological mechanisms. For example, cardioembolic stroke, caused by a blood clot from the heart, may have a different inflammatory profile compared to lacunar stroke, caused by small vessel disease. The location of the stroke can also influence the inflammatory response and its relationship to stroke severity. Strokes involving different brain regions may trigger distinct inflammatory cascades. Inflammation in stroke is not a static event but a dynamic process that evolves over time. The initial inflammatory response, characterized by the influx of leukocytes and the release of pro-inflammatory mediators, is followed by a later phase of resolution and repair. The early inflammatory response, reflected by the TLC measured in our study, may contribute to the initial damage and neurological deficits. The later phases of inflammation, involving the recruitment of macrophages and the release of anti-inflammatory mediators, may play a role in tissue repair and remodeling. In some cases, inflammation may persist chronically, contributing to long-term neurological deficits and disability.[16,17]

The findings of our study, highlighting the distinct inflammatory profiles of hemorrhagic and ischemic stroke, carry significant clinical implications. Recognizing these differences opens avenues for developing targeted therapeutic strategies that address the specific inflammatory challenges posed by each stroke subtype. By tailoring treatment approaches to the unique inflammatory landscape of each condition, we can potentially improve outcomes and enhance recovery for stroke patients. Hemorrhagic stroke, characterized by the rupture of blood vessels and bleeding into the brain, unleashes a potent inflammatory response that contributes significantly to brain injury. Our study, demonstrating a significantly higher TLC in hemorrhagic stroke patients, underscores the need for therapeutic strategies that effectively mitigate this inflammatory cascade. Heme, released from damaged red blood cells, acts as a potent pro-inflammatory molecule in hemorrhagic stroke, triggering oxidative stress and neuronal damage. HO-1, an enzyme that catalyzes the degradation of heme into biliverdin, carbon monoxide, and free iron, emerges as a promising therapeutic target. By breaking down heme, HO-1 reduces its pro-inflammatory and pro-oxidant effects. Biliverdin, a byproduct of heme degradation, possesses antioxidant properties, further mitigating oxidative stress. Carbon monoxide, another byproduct, exerts anti-inflammatory effects by inhibiting the production of pro-inflammatory cytokines. HO-1 also exhibits direct neuroprotective effects by inhibiting apoptosis and promoting neuronal survival. A naturally occurring

porphyrin, hemin has been shown to induce HO-1 expression and reduce brain injury in preclinical models of hemorrhagic stroke. Statins, commonly used to lower cholesterol, also possess HO-1 inducing properties. Clinical trials are underway to investigate their potential in hemorrhagic stroke. Certain natural compounds, such as curcumin and resveratrol, have also demonstrated HO-1 inducing activity and are being explored for their therapeutic potential. Thrombin, a central player in the coagulation cascade, also exerts potent pro-inflammatory effects in hemorrhagic stroke. It activates protease-activated receptors (PARs) on various cell types, triggering the release of inflammatory mediators and exacerbating brain injury. Direct thrombin inhibitors, such as dabigatran and argatroban, directly block thrombin's enzymatic activity, preventing its interaction with PARs and other substrates. By inhibiting thrombin, these agents reduce the activation of PARs, mitigating the downstream inflammatory cascade. Thrombin inhibitors may also offer direct neuroprotective effects by reducing excitotoxicity and apoptosis. Clinical trials are underway to evaluate the efficacy and safety of thrombin inhibitors in hemorrhagic stroke, but their use is currently limited due to concerns about increased bleeding risk. Oxidative stress, a key driver of inflammation and neuronal damage in hemorrhagic stroke, can be targeted with antioxidant therapies. These therapies aim to neutralize reactive oxygen species (ROS) and restore redox balance. NAC, a precursor of glutathione, a potent antioxidant, has shown promise in preclinical studies in reducing oxidative stress and brain injury in hemorrhagic stroke. Clinical trials are ongoing to evaluate its efficacy in stroke patients. Vitamin E, a fat-soluble antioxidant, has also been investigated for its potential in hemorrhagic stroke. While some studies have shown benefits, others have not, and its role remains unclear. Other antioxidants, such as coenzyme Q10 and melatonin, are also being explored for their potential in mitigating oxidative stress in hemorrhagic stroke. Neuroprotective agents aim to protect neurons from damage and promote their survival. Erythropoietin, a hormone that stimulates red blood cell production, also possesses anti-inflammatory and neuroprotective effects. It can reduce apoptosis, promote angiogenesis (new blood vessel formation), and enhance neurogenesis (new neuron formation). Minocycline, a tetracycline antibiotic, has been shown to inhibit microglial activation, reduce inflammation, and exert neuroprotective effects. Other agents, such as citicoline and magnesium sulfate, are also being investigated for their potential in reducing brain injury and improving outcomes in hemorrhagic stroke. In cases of large hematomas or significant mass effect, surgical interventions may be necessary to evacuate the hematoma and reduce intracranial pressure. A craniotomy involves removing a portion of the skull to access the hematoma and surgically remove it. Minimally invasive techniques, such as endoscopic evacuation and stereotactic aspiration, are increasingly being used to minimize surgical trauma and improve outcomes. These techniques involve inserting small instruments through small incisions to access and remove the hematoma. While inflammation also contributes to the pathophysiology of ischemic stroke, the focus shifts from complete suppression to careful modulation. The inflammatory response in ischemic stroke, while detrimental in excess, also plays a role in tissue repair and recovery. Therefore, the goal is to strike a balance, mitigating the harmful effects of inflammation while preserving its beneficial aspects. Cytokines, signaling molecules that mediate the inflammatory response, can be targeted with selective inhibitors. TNF-α, a potent pro-inflammatory cytokine, has been implicated in ischemic stroke pathophysiology. TNF-α inhibitors, such as infliximab and etanercept, have shown promise in preclinical studies in reducing inflammation and brain injury. However, clinical trials have yielded mixed results, highlighting the need for further research to identify optimal therapeutic targets and strategies. IL-1β, another key pro-inflammatory cytokine, is also a potential therapeutic target. IL-1β inhibitors, such as canakinumab and anakinra, are being investigated for their potential in ischemic stroke. Inflammatory

signaling pathways, such as the NF-κB pathway and the inflammasome, can be targeted with specific inhibitors. The NF-κB pathway is a master regulator of inflammation, controlling the expression of numerous pro-inflammatory genes. NF-κB inhibitors, such as BAY 11-7082 and IKK inhibitors, can modulate the inflammatory response without completely suppressing it. The inflammasome, a multiprotein complex that activates caspase-1 and leads to the release of IL-1β, is another potential therapeutic target. Inflammasome inhibitors, such as MCC950 and VX-765, are being investigated for their potential in ischemic stroke. Mild hypothermia, the lowering of body temperature, has shown promise in reducing inflammation and brain injury in ischemic stroke. Hypothermia can slow down metabolic processes, reduce oxidative stress, and attenuate the inflammatory response. It can also reduce excitotoxicity and apoptosis, protecting neurons from damage. Clinical trials are ongoing to evaluate the efficacy and safety of hypothermia in stroke patients. However, the optimal duration and target temperature for hypothermia remain to be determined. Stem cell therapy, the transplantation of stem cells into the injured brain, is being explored as a potential therapeutic strategy for ischemic stroke. Stem cells can differentiate into various cell types, including neurons and glial cells, potentially promoting tissue repair and recovery. They can also release growth factors and other trophic factors that support neuronal survival and function. Various types of stem cells, including mesenchymal stem cells, neural stem cells, and induced pluripotent stem cells, are being investigated for their therapeutic potential in ischemic stroke. Rehabilitation, including physical, occupational, and speech therapy, plays a crucial role in stroke recovery. Physical therapy can help to improve motor function, strength, and balance. Occupational therapy can help to improve cognitive skills, such as attention, memory, and problem-solving. Speech therapy can help to improve communication skills, including speaking, understanding, and reading. The recognition of distinct inflammatory profiles in hemorrhagic and ischemic stroke paves the way for personalized medicine, tailoring treatment strategies to the individual patient's needs. Identifying biomarkers that predict the inflammatory response and the risk of complications can help to guide treatment decisions. For example, elevated levels of C-reactive protein or specific cytokines may indicate a more pronounced inflammatory response and a higher risk of poor outcomes. Advanced imaging techniques, such as PET and MRI, can provide insights into the inflammatory response and the extent of brain injury, helping to guide treatment decisions. Genetic profiling can identify individuals who may be more susceptible to severe inflammation or complications, allowing for proactive interventions.[18-20]

5. Conclusion

This study demonstrated a significantly higher total leukocyte count (TLC) in hemorrhagic stroke patients compared to ischemic stroke patients, indicating a more pronounced early inflammatory response in hemorrhagic stroke. This difference likely reflects the unique pathophysiology of hemorrhagic stroke, with the extravasation of blood and its components triggering a cascade of inflammatory events. While no significant correlation was found between TLC and stroke severity (NIHSS score) in either group, this study underscores the importance of considering the distinct inflammatory profiles in hemorrhagic and ischemic stroke. Future research should explore the prognostic value of TLC and other inflammatory markers, and investigate targeted therapies aimed at modulating inflammation to improve outcomes in stroke patients.

6. References

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