DISSERTATION FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PHD)

HEMATOLOGIC INDICES IN ACUTE ISCHEMIC STROKE

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1. Abbreviations

ACA: Anterior cerebral artery

ACE: Angiotensin converting enzyme

ACHA: Anterior choroidal artery

ADP: Adenosine diphosphate

AICA: Anterior inferior cerebellar artery

AIS: Acute ischemic stroke

aSICH: Asymptomatic intracerebral hemorrhage

ASPECTS: Alberta Stroke Program Early CT Score

ATP: Adenosine Triphosphate

AUC: Area under the curve

BA: Basilar artery

BBB: Blood brain bar

BMI: Body mass index

CAD: Coronary artery disease

CCL: CC-chemokine ligand

CCR: CC-chemokine receptor

CI: Confidence interval

CT: Computed tomography

CTA: Computed tomography angiography

CXCL: CXC-chemokine ligand

CXCR: CXC chemokine receptor

DAMPs: Damage associated molecular patterns

DM: Diabetes Mellitus

ECASS: European Cooperative Acute Stroke Study

EDTA: Ethylenediaminetetraacetic acid

FPR: Formyl peptide receptor

HMGB1: High mobility group box 1

hsCRP: High-sensitivity C-reactive protein

HSP72: Heat shock protein 72

HT: Hypertension

ICA: Internal carotid artery

ICH: Intracerebral hemorrhage

ICAM-1: Intracellular adhesion molecule-1

IL: Interleukin

ILR: Interleukin receptor

IS: Ischemic stroke

IQR: Interquartile range

I.V: Intravenous

LMR: Lymphocyte–monocyte ratio

LSA: Lenticulostriate artery

MAC-1: Macrophage 1 antigen

MCA: Middle cerebral artery

MCP-1: Monocyte chemoattractant protein-1

MDM: Monocyte-derived macrophages

ME: Mixed effect

MMP: Matrix metalloproteinase

MMP-9: Matrix metalloproteinase 9

MOOSE: Meta-analysis of Observational Studies in Epidemiology

MPL: Myeloproliferative leukemia protein

MPO: Myeloperoxidase

MPV: Mean platelet volume

MRI: Magnetic resonance imaging

MRS: Modified Rankin Scale

MI: Myocardial infarction

MIP-1: Macrophage inflammatory protein-1

NADPH: Nicotinamide adenine dinucleotide phosphate

NCCT: Non-contrast computerized tomography

NIHSS: National Institutes of Health Stroke Scale

NLR: Neutrophil–lymphocyte ratio

NOS: Newcastle-Ottawa Scale

PAD: Peripheral artery disease

PAF: Platelet-activating factor

PC: Platelet count

PCA: Posterior cerebral artery

PCT: Platelet-activating factor

PDW: Platelet distribution width

PFO: Patent foramen ovale

PICA: Posterior inferior cerebellar artery

PICH: Primary intracerebral hemorrhage

PICOS: Patient Population of Problem, Intervention, Comparator, Outcome and Setting

P-LCR: Platelet large cell ratio

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RE: Random effect

ROC: Receiver operating characteristic

ROS: Reactive oxygen species

rt-PA: Recombinant tissue plasminogen activator

SD: Standard deviation

SICH: Symptomatic intracerebral hemorrhage

SMD: Standardized mean differences

TIA: Transient ischemic attack

TLR: Toll-like receptor

TNF: Tumor necrosis factor

TNFa: Tumor necrosis factor alpha

TPO: Thrombopoietin

TOAST: Trial of ORG 10172 in Acute Stroke Treatment

TXA2: Thromboxane A2

VD: Vascular disease

WBC: White blood cell count

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2. Acknowledgement

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3. Introduction

Stroke is one of the predominant causes of mortality and morbidity in the world, with incidence rates that vary by region. Platelets have been identified as crucial participants in the pathophysiology of atherothrombosis and ischemic stroke, marker such as, Mean Platelet Volume (MPV) can assess platelet turnover. Elevated MPV, which is generally associated with more immature and bigger platelets, is associated with an amplified risk of thrombosis.

Meanwhile, despite significant advances in treatment, acute ischemic stroke (AIS) still poses a substantial burden, with recombinant tissue plasminogen activator (rt-PA) being a frequently used therapeutic method. Personalizing AIS care is critical because thrombolysis does not assist all patients and others may experience severe effects, including intracerebral hemorrhage. The Neutrophil-Lymphocyte (NLR) and Lymphocyte-Monocyte Ratio (LMR), which are generated from standard complete blood count tests, have emerged as possible prognostic markers for AIS outcomes, providing quick and easy insights.

Given the diversity in findings across prior research, this study intends to shed light on the association between MPV, Platelet Count (PC), and atherosclerosis. In addition, we look into the possible relationship between NLR and LMR and prognosis of patients with AIS after thrombolysis.

4. Background of ischemic stroke

Stroke can be divided into two main general types: ischemic stroke and hemorrhagic stroke, which latter group comprises subarachnoid hemorrhage and intracerebral hemorrhage. It is a conspicuous cause of mortality and disability worldwide. According to American Heart association Ischemic stroke (IS), account for 87% of all stroke subtypes globally. Ischemic stroke is characterized by infarction of the central nervous system: brain, spinal cord, or retina [1,2]. Because of advancements in technology, specifically in radiological imaging, the description of ischemic stroke has drifted from a predominantly clinical assessment to a

classification based on tissue characteristics. Many cases with transient neurological symptoms with full clinical recovery in the presence of parenchymal damage on brain MRI are classified as stroke. When blood flow is temporarily interrupted, a transient ischemic attack (TIA) occurs, where both blood flow as well as appeared symptoms get resolved before causing any permanent damage.

The pathogenesis of TIA is indistinguishable to that of ischemic stroke, as well as the inquiries into the root cause and strategies for secondary prevention.

Very early studies in 1868 and another pivotal research conducted in the 1970s unveiled a groundbreaking revelation: a substantial portion of the initial clinical impairments observed in stroke patients can be attributed to insufficient blood perfusion in the region surrounding the ischemic core known as the ischemic penumbra, which lacks electrical activity [3, 202]. If perfusion is not resorted, this penumbral area undergoes a transformation into irreparably damaged tissue, just like the ischemic core. The pace of this progression, however, exhibits significant variability among individuals [3].

This penumbral brain area, however, has the potential for rescue and the restoration of its normal function through swift reperfusion. Ever since the publication of the inaugural successful trial of thrombolysis in stroke patients in 1995, this pivotal revelation has underpinned the development of treatments [4]. Consequently, there have been a revolution in the outcomes for individuals afflicted by stroke.

Patients with ischemic stroke are presently best managed geologically in the specific stroke division. These centers are facilitated by an experienced interdisciplinary health care team and clinicians follow the best-evidence stroke guidelines [5]. Thrombolytics given intravenously can reduce disabilities when treatment is administered within time frame of 270 minutes from beginning of stroke [6]. In the certain cases, a favorable brain perfusion CT/MRI examination

might enable intravenous thrombolysis (IVT) up to 540 minutes from stroke onset, including wake-up stroke cases [7-9].

Mechanical clot retrieval via catheter angiography, also known as Endovascular thrombectomy, results in a more than twofold decrease in disabilities for a wide range of patients with large blood vessel occlusion. This holds true if the procedure is conducted within 360 minutes from the beginning of onset of symptoms [10], which even could be extend up to 24 hours post-stroke for patients selected using brain perfusion imaging [11, 12]. Nevertheless, it is essential to acknowledge that both intravenous thrombolysis and endovascular thrombectomy share a common constraint, which is time. Addressing this time-related challenge is of paramount importance in order to optimize the advantages of these therapies within healthcare systems and expedite treatment [6, 13].

4.1. Epidemiology of ischemic stroke

Across the globe roughly 14 million people are affected by stroke each year. It is the secondary leading contributor to mortality, accounting for approximately five million deaths per year [14, 15]. According to estimations 25% of adult population will experience episode of stroke in their lifetime, more over there are more than 80 million stroke survivors worldwide [1, 15].

Secondary preventive measures are centered on high-risk demographic of stroke survivors. Ischemic stroke prevalence and incidence have changed throughout time. There were 9.5 million ischemic stroke incidents worldwide in 2016 [1, 14]. 2.7 million People died in 2017 as a result of ischemic stroke [16] (Figure 1). Over the 1990–2013 time-frame, ischemic stroke's prevalence, mortality, and disability-adjusted life years all dropped globally [17]. In years 1990 to 2005 there was an increase, then fell from 2005 to 2013, and finally there was a small statistically not significant rise in the worldwide stroke incidence from 1990 to 2013 [17].

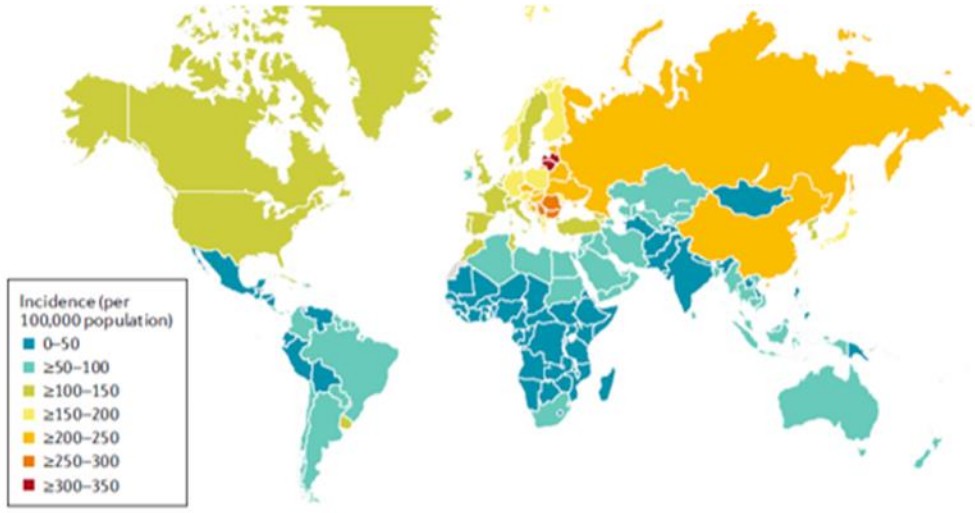


Figure 1. Global Burden of Disease Cause of Death Collaborates. Distribution of incidence of Ischemic stroke by different countries (Lancet, 2018).

A more than twofold decrease in fatalities due to stroke can be attributable to remarkably improved preventive measures. It is interesting to point out that between years 1990 and 2010, the epidemiology of ischemic stroke altered depending on the economy of a nation. For instance, nations with higher income had declines in prevalence of death rate, disabilities and lower mortality-to-incidence ratio. On the other hand, in case of low- and middle-income nations there was no appreciable variations in this period of time [18]. These discrepancies may result from variations in the population's age distribution, life expectancy, health state, and standards of healthcare delivery.

4.2. Risk factors of ischemic stroke

Age, gender, and inherited factors are amongst the ischemic stroke risk factors that cannot be changed. The consequence of advancing age as a risk factor for ischemic stroke varies, depending on a country's level of advances. In developed countries incidence of stroke had a greater rise after age 49 whereas in developing countries the prevalence of stroke was seen after age 39 [17]. The prevalence of ischemic stroke has increased approximately by 37% in related disability-adjusted life years in those aged 20 to 64 worldwide between 1990 and 2013 [19]. According to a survey from 2013, men had a greater incidence of ischemic stroke than women [20].

Most incidences of ischemic stroke are sporadic, despite the fact that some monogenic causes have been found. Using genome-wide complex trait analysis, the inheritance of ischemic stroke is predicted to be 37.9% [21]. There are several modifiable ischemic stroke risk factors. The INTERSTROKE study found out that globally 10 variables were constantly concomitant with ischemic stroke across geographic provinces, gender, and age categories. These variables are responsible for approximately ninety-one percent of the population risk attribution for ischemic stroke [22]. History of hypertension (HT), inconsistent physical exercises, an elevated apolipoprotein B -to- apolipoprotein A1 ratio, unhealthy diet, an excessive waist/hip ratio, psychological stress, smoking, cardiac conditions (atrial fibrillation and prior myocardial infarction), excessive consumption of alcohol, and diabetes mellitus (DM) were among the risk factors.

Hypertension was associated with the highest risk (OR 3.14, 99% CI 2.67-3.71) and a population-attributable risk of 45.2% (99% CI 40.3-50.0%). Sleep apnea, none acute inflammation, gum disease, and chronic renal illness are all potential risk factors [23]. Furthermore, in a few studies exposure to air pollution have found links between temporary increases in stroke prevalence [24].

4.3. Mechanism/patho-physiology of ischemic stroke

The vast majority of ischemic strokes are due to formation of thromboembolism, either by formation of atherosclerosis in the large arteries or/and cardiac conditions. Regarding the cardiac source of embolism, atrial fibrillation chiefly serves as its usual source. Disease in the small arteries (more common in Asia) which is connected to HT and DM, Vasculitis, dissection of arteries, paradoxical embolism through patent foramen ovale (PFO), and hematological diseases are considered as another causes of ischemic stroke [25] (Table 1). The identification of the origin of an ischemic stroke is of great importance due to the fact that it could direct physician to different therapeutic approaches in order to avoid further strokes.

Etiology	Investigation
Atherosclerosis	Computed Tomography angiography Magnetic resonance angiography Carotid Doppler ultrasound
Cardioembolism	Holter/loop recorder Echocardiography
Small vessel disease	Brain magnetic resonance imaging
Arterial dissection	Computed Tomography angiography Magnetic resonance angiography T1 fat saturated neck Magnetic resonance imaging
Cerebral vasculitis	Computed Tomography angiography Magnetic resonance angiography Catheter angiography Cerebrospinal fluid examination Brain and leptomeningeal biopsy
Reversible cerebral vasoconstriction syndrome	Computed Tomography angiography Magnetic resonance angiography Catheter angiography
Moyamoya disease	Computed Tomography angiography Magnetic resonance angiography Catheter angiography
Fabry disease	Magnetic resonance imaging Blood spot enzyme test
Antiphospholipid syndrome	Lupus inhibitor assay Anti-cardiolipin IgG assay Anti β_2- glycoprotein antibody assay
Sickle cell anemia	Blood film Hemoglobin electrophoresis
Polycythaemia vera	Hemoglobin measurement Hematocrit measurement JAK2 mutation status
Essential thrombocytosis	Platelet count JAK2 mutation status

Table 1. The causes of stroke and related investigations. (Bruce C. V. Campbell, Deidre A. De Silva, Malcolm R. Macleod et al, the cause of stroke determines the strategy for prevention of recurrent stroke. Nature Reviews Disease Primers., 2019).

5. Atherosclerosis as an arterial cause of stroke

In the presence of atherosclerosis within the cerebral vasculature, there is a possible scenario where the lipid core within atherosclerotic plaques might be exposed to the circulation, thereby creating a predisposition for the development of thrombi. This exposure is frequently incited by inflammatory mechanisms and the resultant in formation of ulcer within the enveloping fibrous cap. Vessels which are narrowed by atherosclerotic plaques, might be occluded by thrombi or embolize distally in the main vessels associated with stroke. The internal carotid artery (ICA) is where atherosclerotic plaques are more frequently found in western populations. Internal lining of vessels known as intima is thought that, thickens and reduced nitric oxide release. This is linked to low shear stress and causes vulnerability to cholesterol plaque development [26]. Despite the fact that cerebral atherosclerosis is infrequently seen in patients in western countries, it is still far more frequent in Asia [27] and is typically found in heavy smokers and people with DM [28]. In fact, compared to white patients who have 5-10% of strokes [29], Asian patients experience 30-50% of ischemic strokes due to cerebral atherosclerosis. Atherosclerosis makes routine thrombectomy difficult because it is linked to higher re-occlusion rates following thrombectomy. It also necessitates more stenting with a higher risk of complications, especially hemorrhage linked to the use of medications such as antiplatelet therapies to maintain stent patency [30].

6. Cardiac causes of stroke

6.1. Atrial fibrillation

Blood can become stagnant during fast electrical discharge patterns of atrial fibrillation or flutter especially in the left atrial appendage which increases the chances of thrombosis. Cardioembolic ischemic stroke risk is increased by both persistent and intermittent atrial fibrillation [31]. Atrial fibrillation is becoming more common in older and obese population [32]. Chronic HT, ischemic cardiac disease, valvular disease, DM, hyperthyroidism, binge

drinking, and obstructive sleep apnea are additional risk factors for atrial fibrillation [33]. The CHA2DS2-VASc score [34] (Table 2), which considers congestive heart failure (CHF) history, age, stroke/TIA history, gender, DM, HT, and vascular disease ((VD), including prior MI, PAD or aortic plaque)) can be utilized for determination of stroke risk for patients with arterial fibrillation requiring anticoagulation. This score system can serve as a means to assess the likelihood of ischemic stroke in patients diagnosed with atrial fibrillation. Patients with score of 2 or higher are recommended to take oral anticoagulant [200].

CHA_2DS_2-VASc risk factor	points
Congestive heart failure Signs/symptoms of heart failure or objective evidence of reduced left ventricular ejection fraction	**+1**
Hypertension Resting blood pressure > 140/90 mmHg on at least two occasions or current antihypertensive treatment	**+1**
Diabetes mellitus Fasting glucose> 125 mg/dL (7 mmol/L) or treatment with oral hypoglycemia agent and/or insulin	**+1**
Previous stroke, transient ischemic attack, or thromboembolism	**+2**
Vascular disease Previous myocardial infarction, peripheral artery disease, or aortic plaque	**+1**
Sex category (female)	**+1**
Age 65-74 years	**+1**
Age 75 years or older	**+2**

Table 2. CHA2DS2-VASc score. **(**Kirchhof, et al, Clinical risk factors for transient Ischemic attack, stroke and systemic embolism in the CHA_2DS_2-VASc score. Eur. Heart Journal 2016).

6.2. Patent foramen ovale

Foramen ovale in the heart during pregnancy permits oxygenated placental blood to bypass pulmonary circulation. There is an increase in left atrial pressure after birth, which in turn results in the closure of the foramen ovale. However, in 25% of the population, foramen ovale exists as a residual patency (a PFO) [35]. Paradoxical embolism and ischemic stroke may result because of this patency. There was a considerable drop in the risk of subsequent ischemic stroke with endovascular PFO closure which has attracted attention to its implication in young stroke patient [36, 37, 38].

6.3. Hematological Causes

Ischemic stroke has a few important but uncommon causes, including hematological diseases [39]. Three of the more prevalent hematological diseases that enhance the risk of thrombus

formation are essential thrombocytosis, polycythemia vera, and antiphospholipid syndrome. The presenting symptom of these illnesses can be a stroke [25] (Table 1). Moreover, sickle cell anemia can result in stroke which is a significant factor in pediatric stroke in people of African heritage [40].

7. Diagnosis, screening and prevention of ischemic stroke

7.1. Non-contrasted Computed Tomography

Sensitivity of native computed Tomography (CT) examination of the brain is near-perfect for detecting extra parenchymal and parenchymal hemorrhage. Traditionally in a patient with signs of AIS, thrombolysis treatment decisions have been based on this method of radiological examination, by which hemorrhage is excluded. Positive diagnosis of stroke in some individuals can be achieved based on early ischemic changes such as indistinction between white and grey matter, hypoattenuation of deep nuclei, and cortical hypodensity with parenchymal swelling.

However, these symptoms may go undetected in the initial hours following the onset of a stroke due to the difficulties in distinguishing between the loss of grey matter and white matter [41].

7.2. CT angiography and CT perfusion

CT perfusion enables the assessment of static acquisition and a time-resolved series of cerebral vasculature following the infusion of an iodinated contrast agent. If arterial atherosclerosis or artery dissection is identified, CT angiography can diagnose ischemic stroke, providing valuable insights into the stroke's pathogenesis due to its accuracy in detecting arterial stenosis and occlusion. All patients diagnosed with ischemic stroke should routinely have CT angiography from arch of aorta to the cerebral vertex in order to determine suitability for endovascular thrombectomy. The degree of collateral flow can also be evaluated by CT angiography which adds more prognostic data about the expected severity of tissue damage [42]. Functional scan of brain is characterized by CT perfusion [25]. CT perfusion is more

frequently implemented as a diagnostic tool to identify the ischemic penumbra due to the availability of many automatic software methods.

7.3. Magnetic Resonance Imaging

Perfusion and diffusion Magnetic Resonance Imaging (MRI), along with T2-based sequences, are just a few examples of the numerous MRI sequences available. These can be used to evaluate a wide range of functional and structural features of brain parenchyma. The utmost sensitive imaging technique for the identification of acute ischemia is diffusion MRI. This method measures the mobility of random molecules of water. Diffusion is constrained in areas with cytotoxic oedema, where the water distribution has shifts from extracellular to intracellular compartments. Within minutes of onset of an ischemic stroke, diffusion MRI appears abnormal [43], and regions with diffusion restriction rarely regain their original appearance [44]. Ionic and vasogenic oedema develop during the subsequent days (18-96 hours) as a result of more blood-brain barrier damage, and it can be seen on both native CT as well as some MRI sequences [45].

8. Management of acute ischemic stroke

8.1. Antiplatelet therapy

Use of aspirin within the first 48 hours of symptoms lowers the prevalence of further strokes and improves treatment results [46, 47]. Although the benefit is less compared to other reperfusion treatments, aspirin is commonly used, and it is also reasonably priced.

Aspirin, when used in conjunction with dipyridamole, or clopidogrel used without aspirin, is somewhat more effective but also more expensive [48]. In patients at high risk, application of aspirin together with clopidogrel within 12 hours of a mild stroke or TIA and continued for around 21 days, decreased the occurrence of recurring stroke [49, 50].

8.2. Reperfusion therapies

8.2.1. Intravenous thrombolysis

Alteplase and Tenecteplase are the two foremost medications which are available for intravenous thrombolysis. A recombinant version of tissue plasminogen activator (rt-TPA), known as alteplase, breaks down plasminogen into plasmin. Then, plasmin breaks down fibrin and removes the thrombus. This treatment is approved globally as a standard thrombolytic therapy after ischemic stroke. Several experiments have assessed the ideal time frame for alteplase delivery [25]. For instance, part A and B studies of NINDS tPA demonstrated a clinical advantage once alteplase was administered within three hours of the start of a stroke [4]. In subsequent experiments, administration of alteplase up to 6 hours after stroke onset showed different degree of benefits [51- 55]. Individual patient data meta-analysis has revealed that the treatment of stroke by alteplase up to 270 minutes following the appearance of symptoms has a substantial therapeutic benefit (a considerable decrease in disability and mortality) [6]. The number of patients that must be treated to successfully treat one more patient over the course of 4.5 hours grows from 4.5 patients within 90 minutes to 15 patients between 3 and 4.5 hours [56]. This result is due to the diminishing amount of recoverable penumbral tissue over time. Moreover, the thrombus' susceptibility to lysis may weaken with time, decreasing the effectiveness of treatment with delayed administration [57].

The most important complication of thrombolysis is hemorrhage, distinctively transformation of ischemic stroke into hemorrhagic stroke. This transformation in extreme situations could exacerbate cerebral injury and enhance the mass effect. In order to be eligible for intravenous thrombolysis beside time frame and radiological imaging proof for salvageable brain, it is important to eliminate any conditions which could increase risk of cerebral or systemic hemorrhage. Patients may be disqualified from receiving thrombolytic therapy for a variety of reasons, including previous cerebral hemorrhage, recent operation, trauma, or systemic

bleeding, usage of anticoagulation medication, coagulopathy, and unrestrained hypertension [58]. Depending on the definition used, there are different risk factors for symptomatic intracerebral hemorrhage.

8.3. Beyond Traditional Approaches

According to recent data, rates of morbidity and mortality are significantly reduced when treatment is initiated within an hour of the onset of symptoms. The Golden Hour is a term used frequently to describe this remarkable 60-minute window following the onset of symptoms, currently rt-TPA stands as the benchmark treatment [4]. About 50% of the patients receiving rt-TPA will either partially or fully recover after three months given the extended time frame of 270 minutes. However, thrombolysis will not be beneficial for a significant portion of patients, and 6-8% of those who receive it will experience an intracerebral hemorrhage that could be fatal. Personalizing acute stroke care, enhance quality of life over lifespan of time, and globally lessen the burden of AIS, it may be important to identify patients in who would benefit from rt-TPA treatment. To accomplish this, it is necessary to develop a prognostic marker for the outcome of thrombolysis, which is quick, affordable, easily accessible, and accurate.

It has been established that thrombocytes play a significant part in the development of atherothrombosis and ischemic stroke. Platelet turnover is measured by mean platelet volume. Platelets with more granules tend to be more immature and thus larger, emitting a greater quantity of chemical messengers, which promote further platelet aggregation and stimulation. The risk of thrombosis increases when the MPV and PC are both elevated. It has been discovered that patients with pulmonary embolism have isolated elevated PC and substantially increased MPV. It has been suggested that altered platelet functions in patients with either type of stroke result in a hypercoagulable state [14]. Both PC and MPV, in primary intracerebral hemorrhage were linked to poor outcome. According to some studies patients with AS have

substantially higher MPV or PC than controls [16, 17], while other studies reported a lower MPV or PC values in patients with AS. Nevertheless, some investigations found no correlation between these parameters and AS.

9. Thrombocytes

The smallest and most reactive of all the blood cells are thrombocytes. These cells are primarily involved in maintenance of normal hemostasis and fibrosis. Their multifunctionality has been sufficiently supported by recent investigations. When chemicals like ADP, TXA2, PAF, and inflammatory cytokines (e.g., IL-1, IL-6, TNF alpha) activate platelets, they initially accumulate at the injury site. This leads to changes in shape, pseudopodia formation, release of cytoplasmic granular content, and subsequent aggregation [59], causing fibrosis and inflammation. As per the extensive literature, MPV serves as a highly informative parameter, offering crucial insights into the progression and prognosis of a broad spectrum of pathological conditions. These conditions span cardiovascular diseases, respiratory ailments, Crohn's disease, rheumatoid arthritis, juvenile systemic lupus erythematosus, DM, and most of malignant neoplasms [60].

During thrombocytopoiesis, platelets are produced as non-nucleated, disc-shaped fragments of megakaryocyte cytoplasm. This complex process is intricately connected with the presence of thrombopoietin (Tpo), ultimately leading to the formation of blood platelets. Megakaryocytes undergo cell proliferation, intracellular platelet protein production, and a loss of proliferative potential when their c-MPL receptor for Tpo is activated [61]. Following that, the repeated processes of endomitosis result in the construction of the polypoidal nucleus of the megakaryocyte [61], which enhances cell metabolism and results in the formation of the system of membranes, cell organelles, and specialized granules required for normal platelet formation [62]. The ploidy level of the megakaryocytes determines the quantity and size of the generating platelets. The more cytoplasm and distinct platelet structure a megakaryocyte nucleus contains,

the higher its ploidy. Proplatelets are formed by an activated cell's cytoplasmic processes that resemble pseudopodia and serve as an intermediary form between megakaryocytes and thrombocytes [63]. Proplatelets are lengthy megakaryocyte cytoplasmic processes that include organelles which are characteristic of thrombocytes but lack definite boundary zones. Because mature proplatelets are smaller than stem cells, they can move to peripheral arteries after being released into bone marrow vessels. Proplatelets may even be hundred times bigger than blood platelets, indicating that their cytoplasm has already begun to fragment in order to give rise to platelet [64].

Tpo is primarily responsible for activating megakaryocytes and increasing thrombocyte release. It has been shown that some inflammatory cytokines can stimulate blood platelet precursor cells in inflammatory conditions [65]. Megakaryocytes are directly affected by IL-6's action via the membranous receptor IL-6R and are also more likely enhance production of Tpo in the liver as a result of this action. This implies that a significant increase in blood PC may occur in an inflammatory condition. The variables that directly influence the ploidy of megakaryocytes, the maturity of progenitor cells, and the activation and wear of blood platelets during coagulation and pro-inflammatory processes determine any variations in the count, total platelet mass, morphology, and function [66]. The lifespan of the Platelets in the blood is 8 to 12 days [67]. About 70% of the total mass of platelets are typically in the circulatory pool in healthy individuals, with the remaining 30% of thrombocytes being stored in the spleen [68].

9.1. Platelets and Inflammatory Response

Leukocytes are drawn to the site of injury during an inflammatory reaction due to the release of cytokines and chemokines by blood platelets. Platelet-leukocyte aggregates are the result of interactions between blood platelets and leukocytes during the inflammatory process [68].

While pro-inflammatory cytokines stimulate megakaryocytes and cause a significant rise in the synthesis and release of thrombocytes, coagulation may cause the count to drop.

9.2. Platelet Morphological Parameters

During a standard blood morphology test, fundamental platelet characteristics are evaluated, providing important data on PC, MPV, platelet distribution width (PDW), plateletcrit (PCT), and the percentage of large platelets with MPV > 15 fL (P-LCR). The most recent studies have demonstrated that platelet parameters can help diagnose a patient's overall health and have prognostic significance in particular illnesses [70].

9.3. Mean Platelet Volume and ischemic stroke

Hematological analysts use volume distribution from a standard blood morphology test to calculate MPV, which is a precise measurement of platelet size. While the percentage of large platelets should be between 0.2 and 5.0% of the total platelet population, MPV ranges between 7.5 and 12.0 fL [71]. In physiological settings, MPV is negatively correlated with platelet count, which is connected to maintaining both hemostasis and consistent platelet mass [72]. This physiological proportion is distorted in several illnesses.

Changes in the ratios of MPV and PC could result from abnormally or noticeably accelerated thrombocytopoiesis, increased wear, or the effect of activating agents on blood platelets [73]. As a result, it has been suggested that these criteria might be used in diagnosis of some disorders. Additionally, MPV is considered as a sign of platelet activity because it corresponds with platelet activity [74]. Those with greater MPV (>15 fL) tend to be younger and have higher levels of reactivity than people with MPV in the reference range. They are produced as a result of megakaryocytes being activated by cytokines, which increases their ploidy and encourages the release of larger platelets [75]. Moreover, it is hypothesized that big thrombocytes have more cell granules, express adhesion molecules more strongly, and activate more quickly, leading to platelet hyperactivity and a higher risk of clot formation [76]. Increased platelet aggregation, TXA2 production, and release are all correlated with elevated MPV [77].

9.4. MPV in Inflammation

In healthy individuals, the elevated PC induces the liver to significantly reduce the production of Tpo through a feedback mechanism, which in turn triggers platelet release by megakaryocytes to maintain continual platelet mass. Nevertheless, the rising levels of proinflammatory cytokines, particularly IL-6, in patients with persistent inflammation can trigger platelet release. This is connected to how IL-6 directly affects megakaryocytes and how it stimulates the production of Tpo. Megakaryocytic nuclei's ploidy and cytoplasm volume both increase as a result of IL-6 and as a consequent result in an abundance of blood platelets [78]. The advance of an inflammatory condition is also linked with an increase in the percentage of large platelets, which is most likely due to intracellular synthesis of procoagulatory and proinflammatory factors, granule degranulation, and stimulation of the platelet pool stored in the spleen [79].

9.5. Factors Influencing PC and MPV Values

According to a number of experts, MPV and platelet count should always be evaluated simultaneously because PC and MPV have a nonlinear inverse relation [80]. Other factors, such as ethnicity, gender race, age, and lifestyle may also have a significant impact on MPV and PC [81-85]. Due to genetic variations, PC and MPV have a high heritability of 84% and 75%, respectively [85].

10. Neutrophils

Neutrophils are one of the primary cells to respond to an AIS. They also participate in clot formation, atherosclerosis, and other pathogenesis-related ischemic stroke processes [201]. Many disorders, including IS, diabetic retinopathy, MI, sickle cell disease, renal micro-vasculopathy, transfusion-related acute lung injury and, acute respiratory distress syndrome, have worsened outcomes when associated to neutrophils [86]. They have numerous functions intended to destroy pathogens; however, they also have an effect on several processes which

may cause or facilitate cerebral infarction [201]. Reactive oxygen species (ROS) including superoxide and hypochlorous acid are produced by neutrophils during the phagocytosis process via NADPH oxidase and myeloperoxidase (MPO), respectively [87]. These ROS can directly damage the blood brain barrier (BBB) and possibly brain cells.

Elastase, cathepsin G, Proteinase 3, MMPs elastase, and cathepsin G are some of the proteases that neutrophils produce during the pathogen-killing process of degranulation, which might harm the blood brain barrier (BBB) and brain cells by breaking down extracellular matrix [88]. Proinflammatory cytokines including IL-1, IL-6, IL-8, and TNF-a, as well as chemokines like MCP-1, CCL2, MIP-1alpha, and CCL5 that may exacerbate ischemic brain injury, can also be released by or reacted to by neutrophils. Several neutrophil receptors engage in interactions with damaged endothelium as well as platelets to encourage clotting/thrombosis [89, 90] and atherosclerosis [90, 91] (Figure. 2).

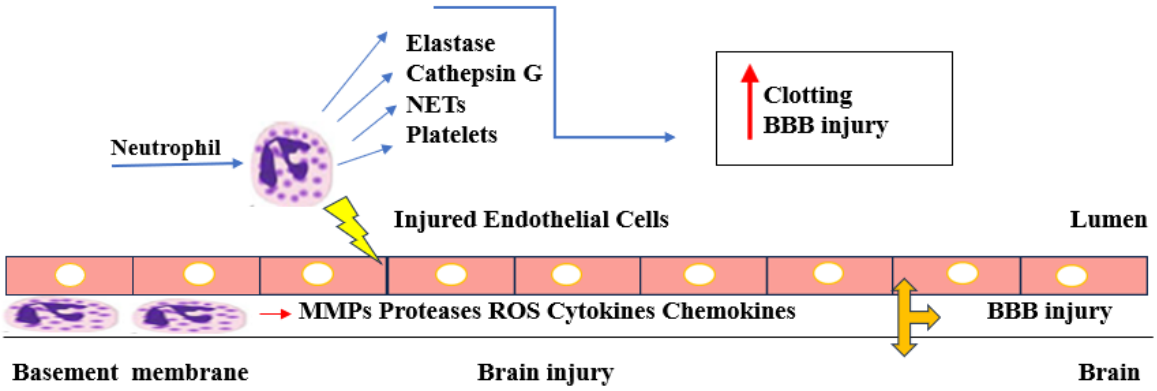


Figure 2. Roles of Neutrophils in Stroke.

Following ischemia, neutrophils arrive within 6-12 hours' time frame to the ischemic brain territory. These leukocytes promote ischemic cerebral injuries in various ways including the release of proinflammatory mediators. [92-94]. Reflow phenomenon happens when flow of

erythrocytes is impaired due to adhesion of white blood cell to the endothelium, disturbing the microvasculature leading to further injury [95].

Activated lymphocytes promote secondly production of ROS, proteases, gelatinases and collagenase by stimulating the endothelium and possibly salvage brain tissues and vessels. Thirdly, creation of biologically active substances may cause vasoconstriction and surge in platelet aggregation. Finally, as result of leukocyte infiltrating into penumbra adjacent to infarct core, further neuronal injury is achieved by the release of proinflammatory cytokines and other immune molecules [96-98].

Several animal studies with lymphocytes have demonstrated a protective effect on nerves, increased lymphocytes repressed inflammatory cytokines including IL-6 or TNF, at the same time, stimulated anti-inflammatory regulation of interleukin 10. According to Cep Juli et al. poor neurological outcome on NIHSS scale was linked to low lymphocyte level. This outcome is explained through activation of renin angiotensin system together with increase in cortisol level post stroke, resulting in apoptosis of lymphocytes [99-100].

At least two different populations of monocytes have been described based on their functions and surface markers. IL-10, acting as an anti-inflammatory cytokine, is produced by classic monocytes, while TNF is produced by "pro-inflammatory" monocytes.

Post ischemic stroke pro-inflammatory monocytes rapidly migrate to site of injury. These cells there then differentiate into macrophages and Dendritic cells. [101-102].

NLR and LMR have shown links with various pathological conditions [103-105], positioning them as potential emerging indicators for assessing inflammation and immune response [106]. Recent investigations have revealed initial signs suggesting a fundamental association between the prognosis of AIS and the levels of NLR and LMR [107, 108]. Significantly, these laboratory parameters can be conveniently extracted from a complete blood count, making them promptly

accessible and valuable markers for clinical use, particularly prior to administration of thrombolytic agents.

11. Meta-analysis in relation to ischemic stroke, PC and MPV

11.1. Protocol and Registration

According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines we conducted our systemic review and meta-analysis [109] in addition to this we verified our study according to the MOOSE (Meta-analysis of Observational Studies in Epidemiology) [110]. The systematic review and meta-analysis protocol was also registered with the PROSPERO database at:

https://www.crd.york.ac.uk/prospero/ display_record.php?RecordID=67864.

11.2. Search Strategy and Study Selection

The suitability criteria conformed to the inclusion standards of the Patient Population or Problem, Intervention, Comparator, Outcomes, and Setting (PICOS) [109]. We made alterations to the PICOS by omitting the 'I' which pertains to Interventions, given that no interventional studies were integrated. Suitable studies were those that met the following requirements: (1) centered on the adult population, (2) encompassed a control group, (3) investigated the diagnosis or assessment of acute stroke, (4) provided comprehensive data on platelet indices in both the patient and control groups, (5) constituted either cross-sectional or case-control studies. There were no restrictions concerning geographic location, language or publication date. Excluded from consideration were abstracts, editorials comments, reviews, and conference proceedings.

Our analysis was founded on the thorough examination of pertinent research published up to July 2017 in, Google Scholar, EBSCOhost, ScienceDirect, Scopus, Web of Science and Medline, In August 2019 we reconducted our search, and incorporated new published data.

Google Scholar was explored through Harzing's Publish or Perish software (Harzing, A.W., 2007, Publish or Perish, accessible at https://harzing.com/ resources/publish-or-perish).

11.3. Data Extraction

Two individuals conducted data extraction using a standard form then cross-validated the information. Any disagreements were resolved through consensus or by engaging in discussions with the tertiary reviewer. We also referenced the bibliographies of the retrieved articles to identify other pertinent studies. All the data was systematically collected. Initially, following the first search, we retained reviews in the list to gather suitable references. In the subsequent phase, we excluded all reviews from the list of accepted publications. The quality of the eligible studies was assessed using the Newcastle-Ottawa Scale (NOS) [111]. The NOS encompasses three domains: the study population's selection, the comparability of groups, and the outcome ascertainment. Articles garnering NOS scores of 6–9 were classified as high quality, while scores of 0–5 indicated poorer quality. In cases where studies only provided median values with a range or interquartile range, we calculated the mean and standard deviation in accordance with Wen et al. [112].

11.4. Data Synthesis and Statistical Analysis

This study was conducted in accordance with the guidelines outlined by Viechtbauer and the work of Huzsvai and Balogh [113, 114]. Our meta-analysis encompassed variations between studies and also included covariates to address potential publication biases. We calculated the Standardized Mean Differences (SMDs) for MP and PC within each individual study. Additionally, we carried out subgroup analysis via a random-effect (RE) meta-analysis to evaluate heterogeneity, considering the type of anticoagulant (EDTA or citrate), the type of analyzer (Sysmex or Coulter), and the type of infarction [Ischemic Stroke (IS)]. Then, a mixed-effect (ME) meta-regression was performed using the type of infarction and type of analytes as the moderator variables. We also conducted an outlier detection for MPV concerning storage

time and type of analyte. Across this study we quantified heterogeneity using the I square (I^2) statistics.

12. Study of Neutrophil lymphocytes ratio and lymphocytes monocytes ratio in relation to stroke

12.1. Study Population

This research enrolled a consecutive group of AIS patients admitted to the Department of Neurology at the University of Debrecen, Hungary, spanning from September 2016 to April 2018. Patient inclusion and exclusion criteria were in accordance with the established standards for intravenous rtPA administration as outlined in the 2008 ESO guideline [115]. The diagnosis of ischemic stroke was definitively confirmed via non-contrast computerized tomography (NCCT) scans and computed tomography angiography CTA. Clinical data, which encompassed the assessment of the National Institutes of Health Stroke Scale (NIHSS) scores, were precisely recorded upon admission and on the first day of hospitalization. Thrombolysis, following the established protocols [115], was executed within the 270 minutes time window commencing from the onset of symptoms through intravenous rtPA application. Patients who underwent mechanical thrombectomy in conjunction with thrombolysis were not within the scope of this study.

On the first day, a control non-contrast CT (NCCT) scan was conducted, and early ischemic changes were determined through the assessment of Alberta Stroke Program Early CT Score (ASPECTS) using evaluations from four independent radiologists [116]. Stroke etiology was classified in accordance with the Trial of ORG 10,172 based on the Acute Stroke Treatment (TOAST) criteria [117]. The presence of intracerebral hemorrhage (ICH) was examined on the first day via NCCT, and patients with hemorrhage were categorized into two groups: symptomatic (SICH) or asymptomatic (aSICH), following the criteria from the European Cooperative Acute Stroke Study (ECASS) II [118].

Assessment of short-term outcomes occurred one day after thrombolysis. A favorable short-term outcome was characterized by a reduction in the NIHSS score by at least four points or a score reaching zero, while an unfavorable short-term outcome was indicated by an increase in the NIHSS score of at least four points [119]. To determine long-term outcomes at ninety days, the modified Rankin Scale (mRS) was used. An adverse outcome was defined as an mRS greater than one (mRS > 1). Our study received approval from the Ethics Committee of the University of Debrecen, Hungary, and the Ethics Board of the Medical Research Council of the Hungarian Ministry of Human Capacities, Hungary. The protocol adhered to the ethical principles of the 1975 Declaration of Helsinki. All patients or their family members provided written consent.

12.2. Blood Sampling and Laboratory Measurements

Peripheral blood samples were obtained prior to the commencement of rt-PA infusion and again 24 hours post thrombolysis. Upon admission, standard laboratory assessments, including ion levels, glucose levels, liver enzymes and renal function test, and high-sensitivity C-reactive protein (hsCRP), were conducted using established techniques (Roche Diagnostics, Mannheim, Germany).

Complete blood counts were analyzed using an automated analyzer (XE 2100, Sysmex Europe GmbH, Hamburg, Germany) from blood samples collected both before and 24 hours after thrombolysis. Hematological parameters were promptly determined following blood collection, and the LMR and NLR were computed from blood samples collected on both occasions.

12.3. Statistical Methods

For continuous parameters, we presented the outcomes either as the mean combined with standard deviation (SD) or as the median accompanied by the interquartile range (IQR) when suitable. Categorical data were conveyed in terms of counts and the associated percentages. To

evaluate multiple groups of continuous data, we utilized one-way analysis of variance (ANOVA) and applied either the Bonferroni post-hoc test or employed Kruskal-Wallis analysis, complemented by the Dunn-Bonferroni post-hoc examination when required.

Categorical data were analyzed through χ^2 or Fisher's exact tests where appropriate. To construct Receiver Operating Characteristic (ROC) curves, we plotted sensitivity against 1-specificity and determined the area under the curve (AUC). Threshold values were derived based on Youden's J statistics. We employed multivariable logistic regression models to evaluate the independent impact of NLR, LMR, their combination, or each leukocyte sub-type count on outcome measures, both before and after adjusting for major baseline characteristics. Significance was defined as a p-value less than 0.05. Statistical analyses were conducted using SPSS 18.0 (Chicago, IL, USA) and MedCalc 14.8.1 software (Mariakerke, Belgium).

13. Aims

1. Investigate the correlation between Acute stroke subtypes and Platelet indices such as MPV, PC.

2. Conduct a meta-analysis of existing research to evaluate differences in laboratory results of MPV, PC in stroke patients as well as in the control groups.

3. Assess the predictive utility of combined NLR and LMR parameters, both before and after the administration of thrombolytics, in a manner distinct from prior investigations.

4. Conduct a comprehensive inquiry into the prospective utility of NLR and LMR as prognostic indicators, aiming to ease clinical decision-making regarding the treatment of AIS.

14. Results of our meta-analysis

Figure 3 illustrates a flowchart detailing the evolution of reviewing process. Initially we identified 6812 studies Subsequently, 2746 duplicates (40.3%) were removed, and 3810 articles (55.9%) were excluded following a review of their titles and/or abstracts. The residual 256 articles underwent eligibility assessment by screening their abstracts and titles, then. thirty-nine studies were chosen for qualitative assessment. We attempted to obtain data from the authors of five studies; however, the data was unavailable. Ultimately, we included thirty-four articles in this meta-analysis [109-111,113-114, 120-148].

Of the studies conducted, three were situated in the United States, while twelve took place in Europe, 10 in Asia, 1 in Africa, and 8 studies had an international focus. The patient populations varied, ranging from 12 to 384 individuals. A significant proportion of the included studies primarily centered on AIS (82%). In 13 studies (38%), no information regarding the type of analyte was reported, and a nearly equivalent number of studies (41%) succeeded in providing details about the type of hematological automated analyzer used (refer to Table 3 and Table 4). For approximately 20.5% of the studies, the elapsed time between blood collection and measurement exceeded 2 hours. Furthermore, a considerable number of studies omitted reporting stroke-related comorbidities (refer to Table 3).

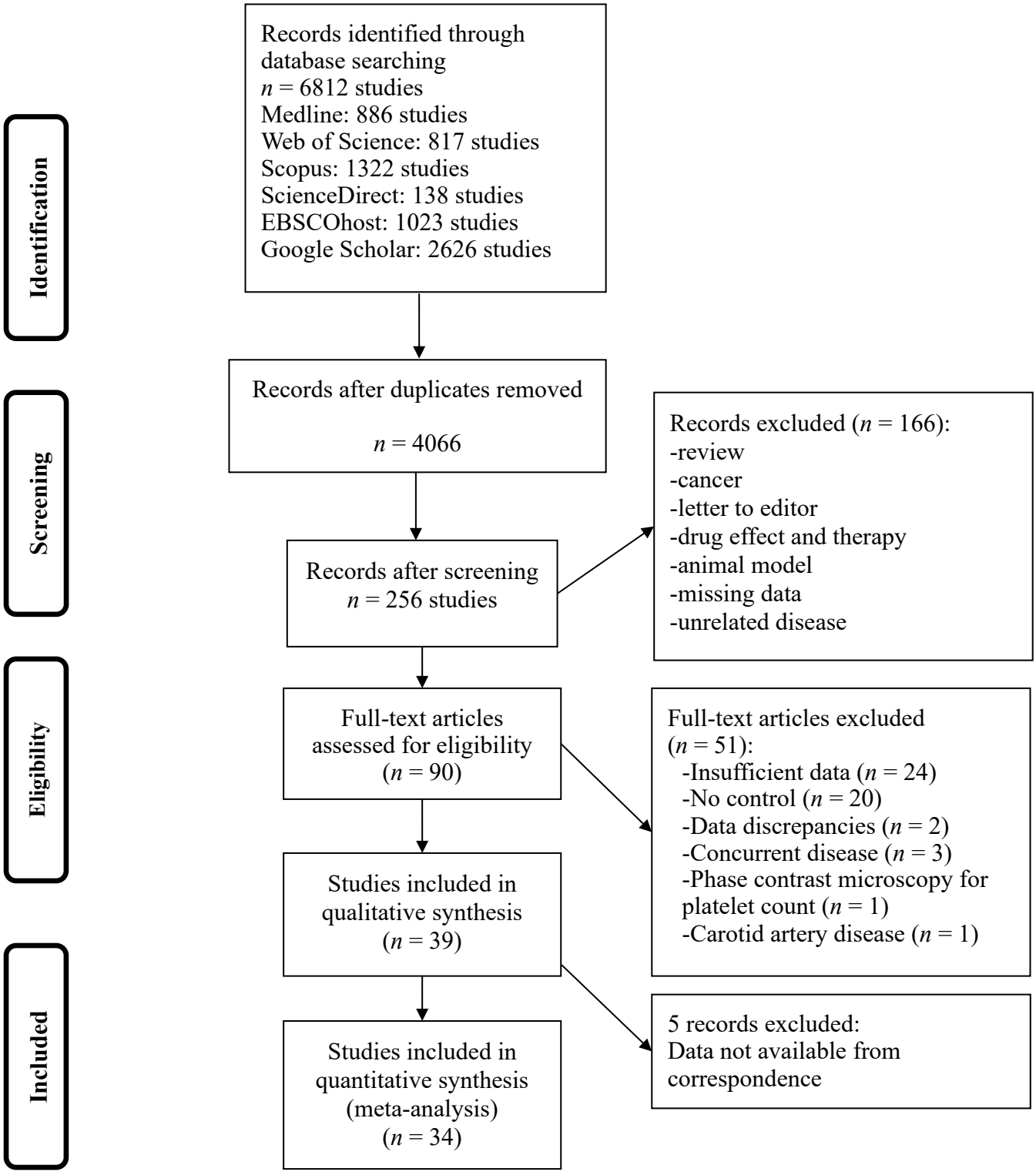


Figure 3. Flow chart diagram presenting the study progression

Author	Year	Country	NOS	Patients				Controls				Patients with history of hyperlipidemia (%)	Patients with history of CAD (%)	Patients with history of DM (%)	Patients with history of HT (%)	Patients with history of smoking (%)	Type of controls	Type of analyte	Sample storage time (min.)	Method of measurement	Type of Infarction
				Age (year)	Number of patients	MPV (fL)	PLT (G/μL)	Age (year)	Number of controls	MPV (fL)	PLT (G/μL)										
1) Farkkila	1987	Finland	8	37.8±5	12	N/A	265±37	35.3±9.8	13	N/A	199±12	N/A	N/A	N/A	N/A	N/A	Healthy	N/A	N/A	N/A	IS
2) D'Erasmo	1990	Italy	9	73±10	36	11.3±1.3	214±66	72±10	60	8.93±0.9	299±61	N/A	N/A	N/A	N/A	N/A	Outpatients	EDTA	240	Coulter	IS
3) D'Erasmo	1991	Italy	6	75±9	44	N/A	215±64	75±9	60	N/A	299±61	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Coulter	IS
4) Falke	1991	Sweden	9	67±8	37	N/A	250±60	61±0.4	46	N/A	239±47	N/A	N/A	N/A	N/A	N/A	Healthy	N/A	N/A	N/A	IS
5) Tohgi	1991	Japan	6	64±12.9	22	9.8±0.8	194±54	55.3±9.5	29	10.7±0.6	247±59	N/A	N/A	N/A	N/A	N/A	Healthy	Citrate	N/A	Sysmex	IS
6) O'Malley	1994	UK	8	79 ±6.5	58	11.3±1.7	255±176	82±8.5	50	10.1±1.8	299±160	N/A	N/A	N/A	N/A	N/A	Healthy	N/A	N/A	N/A	IS
7) Giroud	1995	France	9	63.5±8.5	130	N/A	149±59	63.5±8.5	130	N/A	195±48	8.1	8.4	13.8	68.4	14.5	N/A	N/A	N/A	N/A	PICH
8) O'Malley	1995	UK	9	79.5±6.5	58	11.3±0.8	255±88	82±8.5	50	10.1±0.9	299±80	N/A	54	8.6	29	14	Rehabilitation	EDTA	1440	Sysmex	IS
9) Butterworth	1998	UK	9	71.9±10.8	137	7.3±1.0	N/A	68.5±13	65	7.1±0.7	N/A	N/A	N/A	N/A	N/A	N/A	Healthy	Citrate	2880	Coulter	IS
				71.9±10.8	137	8.0±1.0	231±82	68.5±13	61	7.7±0.8	236±54	N/A	N/A	N/A	N/A	N/A	Healthy	EDTA	2880	Coulter	IS
				68.5±11	25	7.3±1.0	233±80	68.5±13	64	7.1±0.7	236±54	N/A	N/A	N/A	N/A	N/A	Healthy	Citrate	2880	Coulter	PICH
10) Smith	2002	UK	9	73 ±12.8	18	9.7±0.8	225±62	72±7.3	14	9.8±0.6	229±43	N/A	0	0	67	38	Outpatients	Citrate	N/A	Sysmex	IS
				73 ±12.8	6	10.3±0.9	208±41	72±7.3	14	9.8±0.6	229±43	N/A	0	0	67	38	Outpatients	Citrate	N/A	Sysmex	PICH
11) Ziai	2003	USA	7	62±2	43	N/A	220±12	57±3	35	N/A	273±12	N/A	N/A	N/A	65	29	Unrelated disease	N/A	N/A	N/A	PICH
12) Cha	2004	Korea	7	58±8.1	29	N/A	207±5	62.8±14.4	52	N/A	222±50	N/A	17.2	51.7	72.4	72.4	Healthy	Citrate	N/A	N/A	IS
13) Wolf	2005	France	6	70±4.3	159	N/A	214±18	67±4	70	N/A	223±12	26.4	18.9	22	53.5	22	No stroke	N/A	1440	N/A	IS
14) Sadreddini	2007	Iran	9	67±15	100	N/A	217±80	67±15	100	N/A	208±65	N/A	N/A	N/A	N/A	N/A	Healthy	EDTA	N/A	Sysmex	IS
15) Ilhan	2010	Turkey	8	65±11	30	8.7±0.8	N/A	60±8.3	30	8.3±0.8	N/A	N/A	N/A	N/A	N/A	N/A	Healthy	EDTA	N/A	Coulter	IS
16) Mayda-Domac	2010	Turkey	9	65.6±12.6	384	9.9±1.81	281±93	63.2±13.7	208	9.5±3.9	269±70	23.9	34.7	41.4	61.5	19.8	Healthy	EDTA	120	Sysmex	IS
				62.2±13.1	208	9.6±1.7	247±77	63.2±13.7	208	9.5±3.9	269±70	26.4	21.1	29.8	75.4	22.1	Healthy	EDTA	120	Sysmex	PICH
17) Al-Tameemi	2012	Iraq	9	64.7±8.5	25	10.9±1.3	254±76	62.4±9.5	20	11±0.98	235±60	N/A	16	56	68	44	Healthy	N/A	1440	Sysmex	IS

18) Järemo	2012	Sweden	6	74±10	72	N/A	265±84	66±8	24	N/A	260±78	N/A	9.7	15.2	44.4	13.8	Healthy	N/A	90	Coulter	IS
19) Cho	2013	Korea	6	51.5±13	166	8.6±1	N/A	N/A	311	8.6±1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	EDTA	120	Advia	IS
20) Dogan	2013	Turkey	7	68±14	143	9.9±0.9	N/A	58±17	60	9.4±0.8	N/A	22.4	37.1	36.4	77.6	42	Healthy	EDTA	15	Sysmex	IS
21) Celikbilek	2014	Turkey	6	69.5±13.4	70	9.8±1.2	N/A	60±10	70	10.2±1.1	N/A	N/A	N/A	N/A	N/A	N/A	Healthy	N/A	N/A	N/A	IS
22) Li	2014	USA	7	53.3±10.4	375	10.4±1.3	224±59	48.9±10	1840	9.2±1.2	228±59	N/A	N/A	24.8	34.1	36.3	No disease	EDTA	30	Sysmex	IS
23) Wang	2015	China	9	63±11	50	10.5±0.8	214±50	51±12	50	10.2±0.6	221±34	N/A	N/A	N/A	N/A	N/A	Healthy	EDTA	N/A	Sysmex	IS
24) Ciancarelli	2016	Italy	7	72.3±1.1	24	11±0.2	N/A	72.4±1.1	24	9.4±0.3	N/A	N/A	N/A	N/A	N/A	N/A	Healthy	EDTA	120	Sysmex	IS
25) Lee	2016	USA	8	68±6.5	73	N/A	238±56	68±6.6	74	N/A	242±58	N/A	N/A	N/A	N/A	52	N/A	N/A	N/A	N/A	PICH
26) Oz	2016	Turkey	6	63±10	52	8.5±0.9	240±68	57±12	40	8.3±0.8	245±83	N/A	N/A	N/A	N/A	N/A	Healthy	EDTA	30	N/A	IS
27) Özkan	2016	Turkey	9	67±10	74	8.9±1.1	262±61	65.5±11	90	8.3±1	260±48	27	N/A	32.4	43.2	21.6	Healthy	EDTA	30	Sysmex	IS
28) Elsayed	2017	Egypt	9	61±13.5	50	8.99±1.5	266±83	53.6±10.5	20	7.7±0.9	266±61.3	N/A	N/A	N/A	N/A	N/A	Healthy	EDTA	120	N/A	IS
29) Gokdemir	2017	Turkey	8	67.4±10.8	48	9.5±2.4	303±124	66±9.94	46	9.2±2.3	328±85	N/A	N/A	32	N/A	N/A	Healthy	Heparin	N/A	N/A	IS
30) Wan	2017	China	7	63.6±7.5	100	11.3±1.7	188±69	62.7±8.1	80	10.6±1.1	191±72	N/A	N/A	26	64	30	Healthy	N/A	N/A	Symex	IS
31) Ayas	2018	Turkey	7	73±9	67	9.8±1.6	249±78	73±9	67	9.6±1.7	257±73	11.9	36.4	38.8	77.6	17.9	N/A	EDTA	60	Coulter	IS
32) Patel	2108	India	6	58±14	50	9.8±1.2	N/A	58±14	50	8.3±1.1	N/A	N/A	N/A	N/A	N/A	N/A	outpatient	EDTA	60	N/A	IS
33) Farah	2018	Israel	7	68.4	200	8.7±1.2	N/A	N/A	30	9.2±1.3	N/A	N/A	N/A	N/A	N/A	N/A	Healthy	N/A	N/A	N/A	IS
34) Sarkar	2018	India	9	55±7.1	70	12.9 ±1.3	N/A	52±5.4	40	10.5±1.3	N/A	N/A	N/A	N/A	N/A	N/A	Healthy	EDTA	N/A	Sysmex	IS

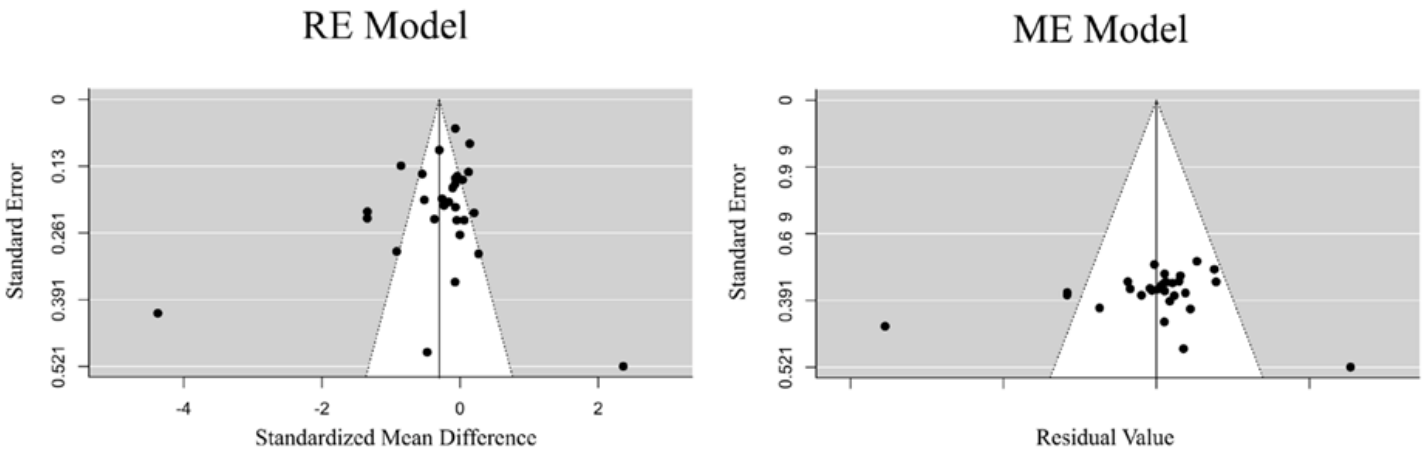
Table 3. Characteristic of included studies. MPV, mean platelet volume; PLT, platelet count; NS, not significant; S, stroke; IS, ischemic stroke; PICH, primary intracerebral hemorrhage; NOS, Newcastle-Ottawa Scale; N/A, not available; CAD, coronary artery disease; DM, diabetes mellitus; HT, hypertension.

Subgroup	No. of Studies	Cases	Controls
Type of Analyte			
EDTA	18	2074	3309
Na-Citrate	6	237	238
Heparin	1	48	46
Not reported	13	1023	702
Type of Analyzer			
Sysmex	15	1657	2827
Coulter	8	548	431
Advia	1	166	311
Not reported	14	1011	726
Type of stroke			
IS	32	2897	3770
PICH	6	485	525

Table 4. Some of characteristics of the studies, ischemic stroke (IS), primary intracerebral hemorrhage (PICH).

To estimate ME and RE models for PC and MPV (Table 5), we utilized the Dersimonian-Laird estimator. The funnel plot highlighted the presence of publication biases in the RE model, particularly regarding MPV. However, the ME model for both variables displayed no evidence of publication biases, as illustrated in Figure 4. We applied a weighted regression model featuring multiplicative dispersion to calculate t-values. Notably, Egger's test detected publication biases in the RE model, specifically for MPV ($p < 0.001$). In the case of PC, t-statistics suggested a more robust symmetry for the mixed-effects model, as indicated in Table 6. Notably, our outlier detection procedure did not reveal any falsely elevated MPV values. To enhance the reliability of both RE and ME models and prevent overfitting due to a limited number of studies, we employed bootstrap sampling, as outlined in Table 7.

A.



B.

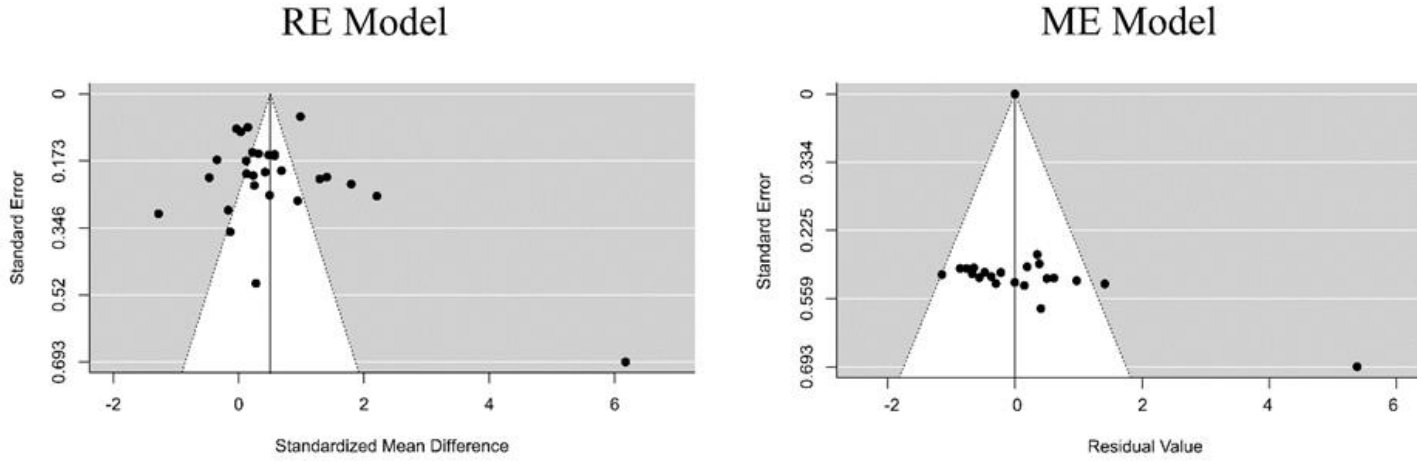


Figure 4. Funnel plot for platelet counts (A) and mean platelet volume (B). [RE = random effect; ME = mixed effect].

Estimation method	MPV				PC			
	RE model		ME model*		RE model		ME model**	
	LL	AIC	LL	AIC	LL	AIC	LL	AIC
DL	-48.48	100.97	-38.54	85.09	-45.42	94.84	-42.02	90.03
HE	-44.55	93.11	-36.67	81.35	-39.44	82.89	-37.48	80.96
ML	-43.67	91.34	-35.48	78.96	-38.94	81.89	-36.86	79.72
REML	-42.71	89.41	-32.56	73.11	-38.16	80.33	-35.41	76.82
SJ	-44.10	92.20	-36.22	80.45	-39.19	82.38	-37.24	80.49

Table 5. Results of the Loglikelihood and Akaike Information criterions for selecting the best model of calculation ME, mixed effect; RE, random effect; DL, DerSimonian- Laird; HE, Hedges estimator; ML, Maximum Likelihood; REML, Restricted ML; SJ, Sidik- Jonkman; MPV, mean platelet volume; PC, platelet count; *, moderator variable is type of analyte; **, moderator variable was type of infarction.

Random effect model	Mixed effect model
Mean platelet volume	
2.46 (0.021)	1.72 (0.100)
Platelet count	
1.00 (0.325)	0.60 (0.553)

Table 6. Egger's regression test of mean platelet volume and platelet count for measuring funnel plot asymmetry*[: t-statistics; p values are given in parenthesis].

Bootstrap estimation	Mean platelet volume		Platelet count	
	Adjusted	Unadjusted	Adjusted	Unadjusted
Effect size (95% CI)	0.86 (0.49–1.43)	0.52 (0.24–0.90)	0.48 (0.32–0.64)	-0.30 (- 0.46–- 0.14)
Heterogeneity (95% CI)	98.05 (97.18–99.48)	97.69 (96.02–98.66)	88.27 (83.18–94.91)	89.07 (84.61–95.77)
Between study variance (95% CI)	1.17 (0.20–1.68)	1.06 (0.51–1.52)	0.21 (0.04–0.29)	0.21 (0.05–0.30)
Bias of effect size	-0.003	0.001	<0.001	- 0.001
Bias of heterogeneity	-0.023	-0.191	0.42	- 0.02
Bias of between study variance	0.014	0.003	0.023	0.023

Table 7. Bootstrap estimation results [95% CI, 95% confidence interval].

14.1. Results regarding PC

Overall, 6107 participants were drawn from 24 publications, with 2492 allocated to the patient group and 3615 to the control group. Three studies indicated that patients with AS exhibited higher PC than controls [122, 133, 134]. In contrast, eleven studies revealed lower PC in the patient group [31-32,121,123-125, 128,130,133,141,149], while eleven other studies found no significant difference in PC between patients and controls (please refer to Table 3,8) [17, 126, 127, 131, 135, 139, 140, 142, 144,145,150]. One study did not provide PC results. The average PC across all publications was 234 G/L (95% CI: 224–244) for patients and 248 G/L (95% CI 238–259) for controls. The ME model indicated a substantial residual heterogeneity for PC [$\chi 2$ = 230.2; df = 27; I2 = 88.3% (95% CI: 80.0–93.1); p< .001]. Regarding ischemic stroke, the estimated pooled mean difference in PC was 0.48 G/L [Z = 1.61; p = 0.107] for the ME model. For the RE model without moderating effects, it was −0.30 (Z = −3.15, 95% CI: − 0.49– −0.11, p = 0.002), as depicted in Figure 5.

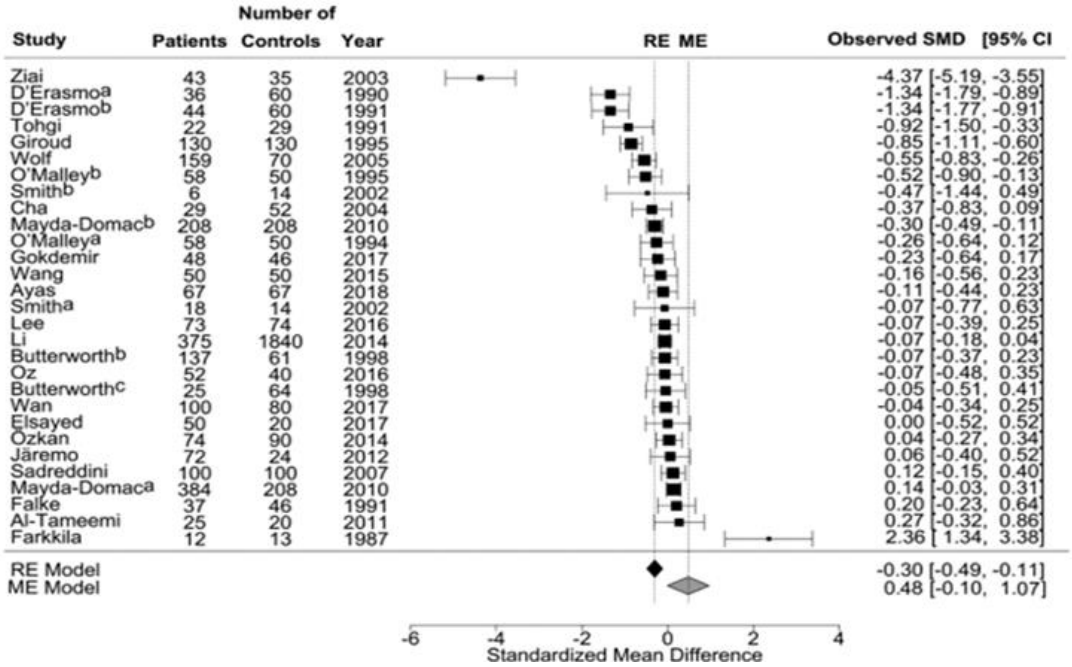


Figure 5. Forest plot of standard mean difference (SMD) for association between platelet count and occurrence of acute stroke

14.2. Results regarding MPV

Out of the twenty-seven studies, seventeen reported that patients with stroke demonstrated greater MPV compared to controls [16, 123, 125, 126, 132, 133, 137, 139-141, 144-146, 148-149]. In contrast, ten studies found no significant difference in MPV between patients and controls [126,127,133,134,143,147,150,204]., interestingly two studies indicated a higher MPV in the control group (Table 3,8) [138,203].

Author	*P* value for MPV	*P* value for PC
1) Farkkila	N/A	NS
2) D'Erasmo	<0.001	<0.001
3) D'Erasmo	N/A	<0.001
4) Falke	N/A	0.0001
5) Tohgi	<0.01	<0.05
6) O'Malley	<0.001	<0.01
7) Giroud	N/A	<0.05
8) O'Malley	<0.001	<0.01
9) Butterworth	0.04	N/A
	0.015	0.63
	0.185	0.43
10) Smith	0.73	0.60
	0.73	0.60
11) Ziai	N/A	0.006
12) Cha	N/A	N/A
13) Wolf	N/A	0.025
14) Sadreddini	N/A	>0.05
15) Ilhan	0.012	N/A
16) Mayda-Domac	0.001	<0.001
	0.964	0.001
17) Al-Tameemi	1.000	1.000
18) Järemo	N/A	NS
19) Cho	>0.05	N/A
20) Dogan	<0.01	N/A
21) Celikbilek	<0.001	N/A
22) Li	<0.001	0.219
23) Wang	0.0128	0.0397
24) Ciancarelli	<0.05	N/A
25) Lee	N/A	0.668
26) Oz	0.53	N/A
27) Özkan	<0.001	0.159
28) Elsayed	0.001	0.482
29) Gokdemir	0.111	0.004
30) Wan	0.002	0.79

Table 8. P values for mean platelet volume (MPV) and platelet count (PC) for included studies

The average MPV across all published studies was 9.8 fL (95% CI 9.4–10.1) for patients and 9.2 fL (95% CI, 8.8–9.6) for controls. Considerable residual heterogeneity was observed in the ME model for MPV [$\chi 2 = 333.5$; df = 20; I2 = 94% (95%CI: 89–97); $p < 0.001$]. Regarding the effect of analyte (EDTA compared to Citrate), the estimated pooled mean difference in MPV was 0.86 ($Z = 5.509$; $p < .001$) for the ME model. In absence of moderating effects, the RE model indicated a mean difference of 0.52 fL ($Z = 4.29$, $p < 0.001$), as depicted in Figure 6.

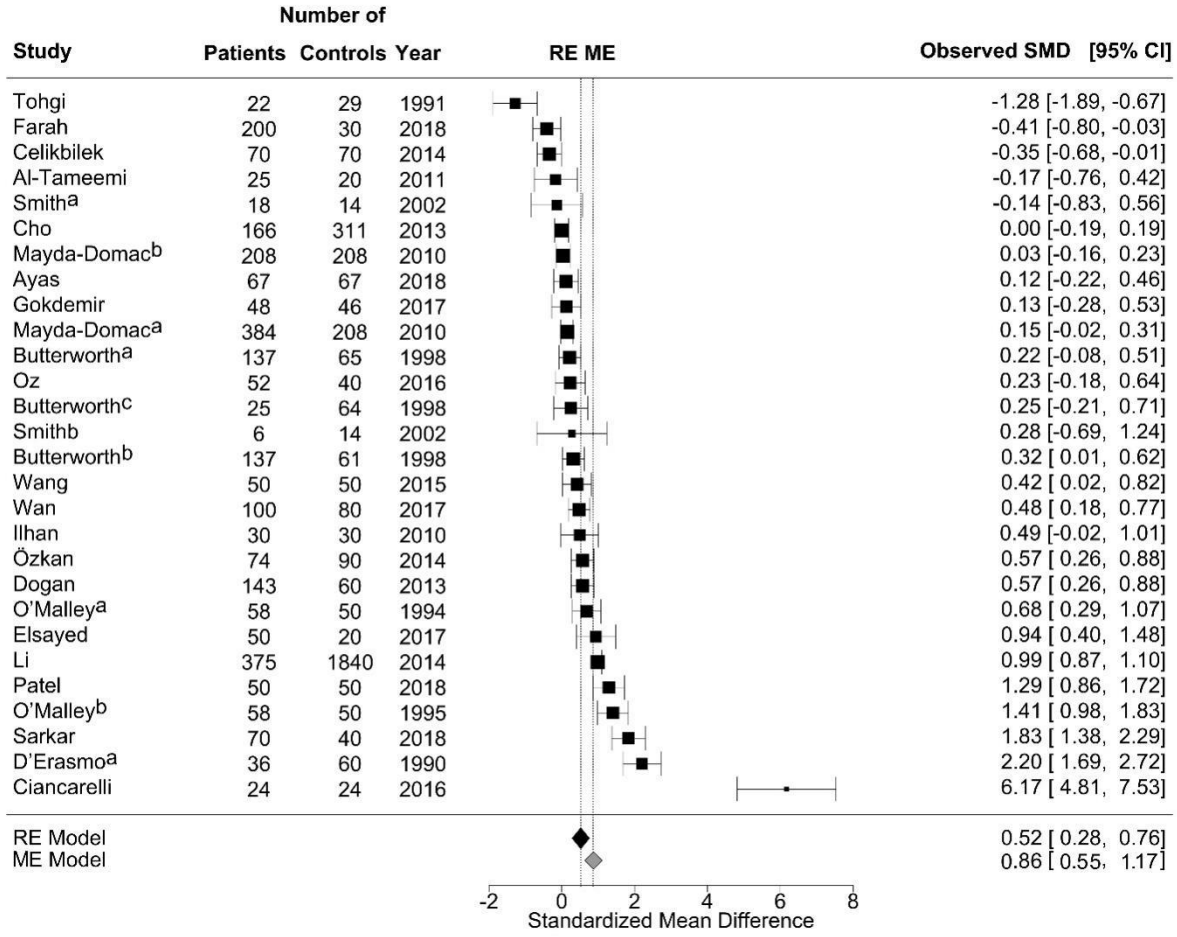


Figure 6. Forest plot of standard difference (SMD) for association between mean platelet volume and occurrence of acute stroke

14.3. Results of subgroup Analysis

We also conducted subgroup and sensitivity analyses to explore the relationship between these parameters, based on the analyte, analyzer, and type stroke for both MPV and PC. In total, twelve studies performed complete blood count measurements in 120 minutes or less, while seven studies assessed blood samples after 120 minutes, and we analyzed these in distinct subgroups. Among the thirty-four studies included in this meta-analysis, three studies had further subdivided their analyses into various subgroups (refer to Table 3) [126, 127, 133]. In the case of AIS, involving twenty-three studies, 2007 cases exhibited significantly lower PC compared to 3090 control individuals (SMD = −0.18; 95% CI: − 0.35 to −0.01, p< 0.001) as depicted in Figure 7a (panel A) and summarized in Table 9.

In the context of PICH, six studies presented more significant findings involving 485 patients compared to 525 controls (SMD = −0.94; 95% CI: −1.62 to −0.25, p< 0.001), as depicted in Figure 7a (panel B) and summarized in Table 9. For PC measurements with citrated samples, the results were significantly higher in 100 patients in comparison to 173 controls (SMD = −0.36; 95% CI: −0.68 to −0.04, p< 0.05). MPV was notably higher among 2444 patients who experienced acute ischemic stroke when compared to 3405 controls (SMD = 0.57; 95% CI: 0.31–0.83, p< 0.001), as illustrated in Figure 7b (panel C) and detailed in Table 10. Conversely, in the case of acute hemorrhagic stroke, MPV was lower in patients compared to controls, but this difference failed to reach statistical significance (SMD = 0.07; 95% CI: −0.10–0.25, p> 0.05), as depicted in Figure 7b (panel D) and summarized in Table 7. MPV measured from EDTA anticoagulated samples was evaluated in seventeen studies, and it was significantly higher among 1974 cases in contrast to 3209 control individuals (SMD = 0.86; 95% CI: 0.55–1.17, p< 0.001). Furthermore, citrated samples from 208 cases exhibited lower MPV compared to 186 controls (SMD = −0.13; 95% CI: −0.69–0.42, p< 0.001).

Across 14 studies utilized Sysmex hematology analyzers, encompassing 2727 controls, notably elevated MPV values were observed in 1557 patients (SMD = 0.64; 95% CI: 0.28–1.01, p< 0.001). In parallel, within six studies featuring Coulter hematology analyzers, 432 patients exhibited markedly increased MPV when contrasted with 347 controls (SMD = 0.58; 95% CI: 0.08–- 1.08, p< 0.001), as indicated in Table 10. Additionally, we explored MPV outcomes in two subcategories based on the time elapsed between venipuncture and analysis, distinguishing between durations exceeding 120 minutes and those less than or equal to 120 minutes (refer to Table 10). Intriguingly, in relation to the control group, MPV displayed significant elevation within both the ≤120-minute and >120-minute groups (SMD = 0.72; 95% CI: 0.36–1.08, p< 0.001) and (SMD = 0.70; 95% CI: 0.08–1.32, p< 0.001), respectively.

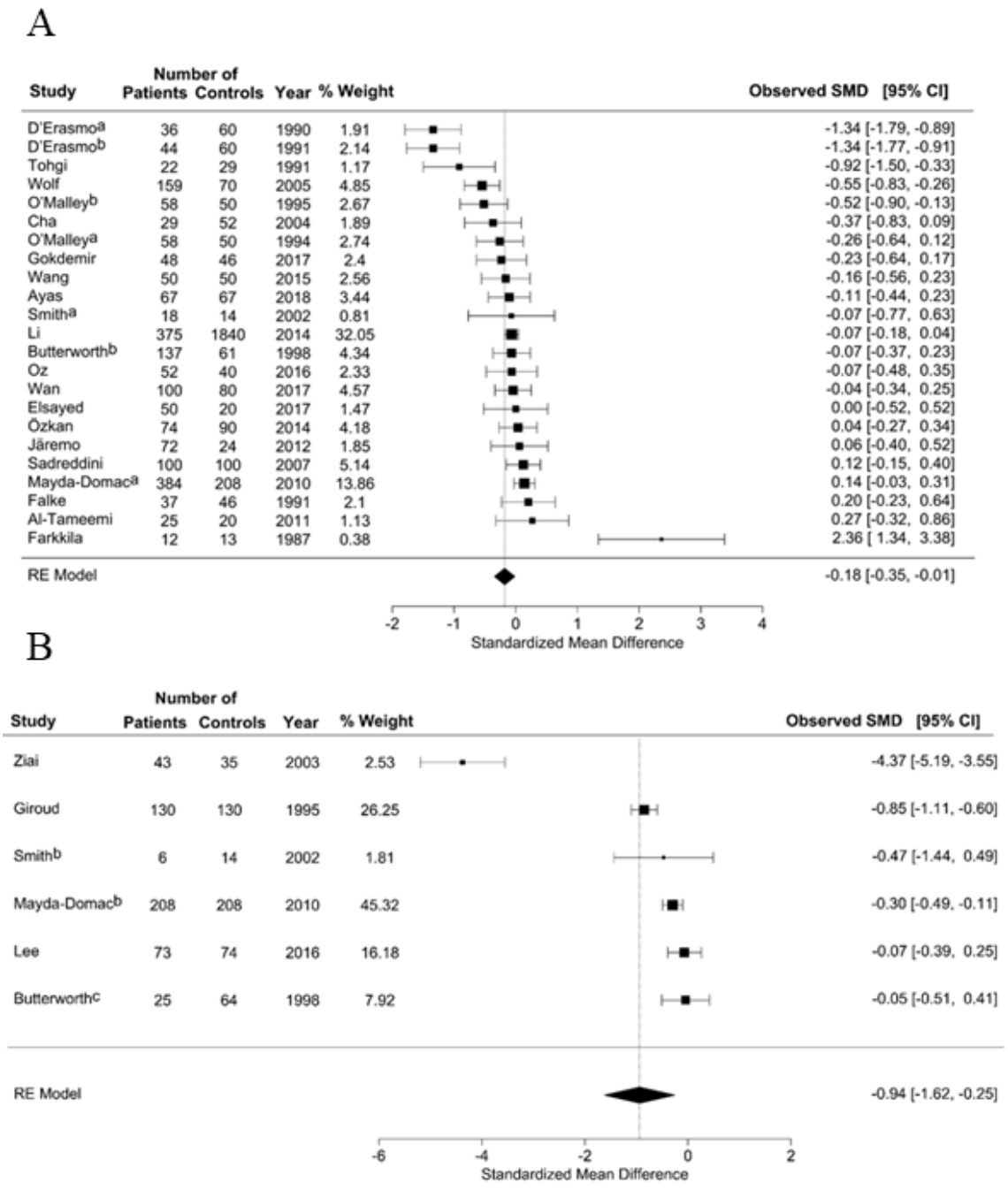
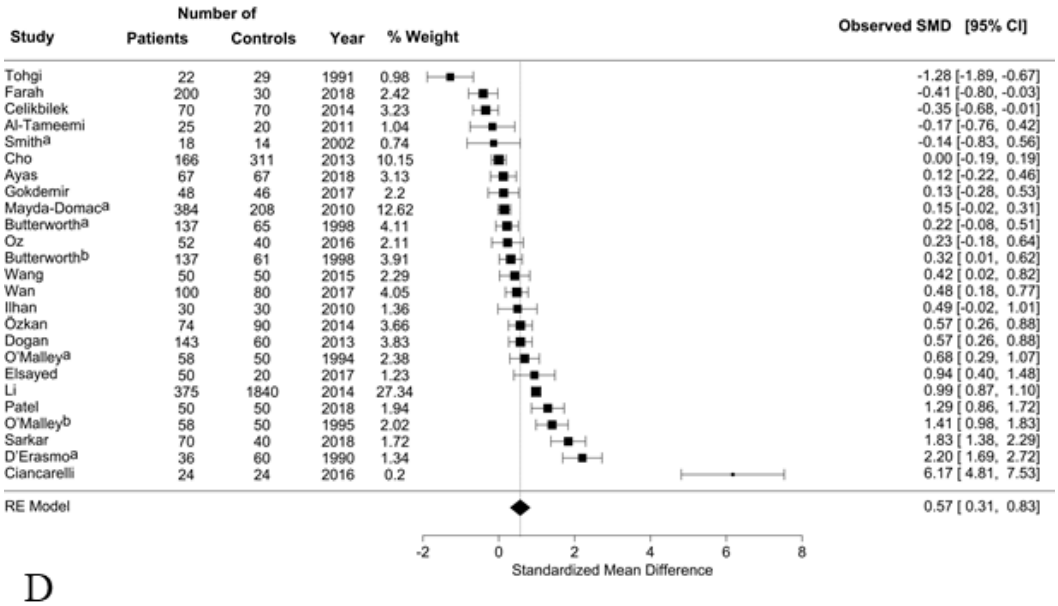


Figure 7a. Subgroup analysis for A- platelet count in patients with acute ischemic stroke, or B- platelet count in patients with acute hemorrhagic stroke.

C



D

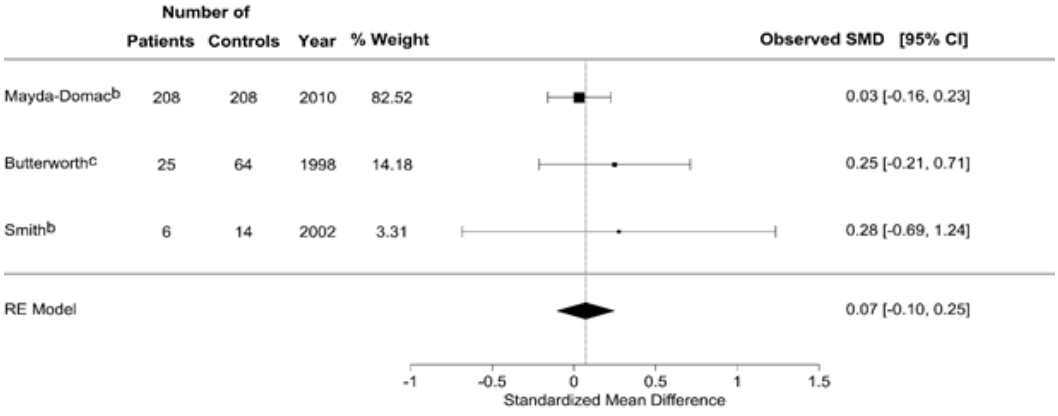


Figure 7b. Subgroup analysis for C- mean platelet volume in patients with acute ischemic stroke, or D- mean platelet volume in patients with acute hemorrhagic stroke.

Subgroup	No. of Studies	Cases	Controls	Difference SMD (95% CI)	I^2% Heterogeneity (95% CI)	$p_{(Het)}$
Type of Analyte						
EDTA	12	1591	2794	− 0.16 (− 0.33 – 0.00)	77 (69,96)	< 0.001
Citrate	5	100	173	− 0.36* (− 0.68 – − 0.04)	33 (0,91)	0.202
Heparin	1	48	46	− 0.23 (− 0.64 – 0.17)	-	-
Not reported	11	753	602	− 0.43 (− 0.93 – 0.07)	94 (86,98)	< 0.001
Type of Analyzer						
Sysmex	12	1420	2703	− 0.11 (− 0.25 – 0.03)	62 (27,93)	0.002
Coulter	6	381	336	− 0.47 (− 0.97 – 0.04)	90 (76,99)	< 0.001
Not reported	11	691	576	− 0.39 (− 0.86 – 0.08)	93 (83,97)	< 0.001
Type of infarction						
Ischemic	23	2007	3090	− 0.18* (− 0.35 – − 0.01)	82 (67,90)	< 0.001
Hemorrhagic	6	485	525	− 0.94** (− 1.62 – − 0.25)	95 (82,99)	< 0.001

Table 9. Random Effect Model Subgroup Analysis for Platelet Count. *, P < 0.05; **, P < 0.01; ***, P < 0.001

Subgroup	No. of Studies	Cases	Controls	Difference SMD (95% CI)	I^2% Heterogeneity (95% CI)	p(Het)
Type of Analyte						
EDTA	17	1974	3209	0.86*** (0.55 – 1.17)	95 (90,98)	< 0.001
Citrate	5	208	186	− 0.13 (− 0.69 – 0.42)	81 (48,98)	< 0.001
Heparin	1	48	46	0.13 (− 0.28 – 0.53)	-	-
Not reported	4	253	220	0.18 (− 0.33 – 0.68)	86 (53,99)	< 0.001
Elapsed Time						
≤ 120 min	11	1593	2918	0.72*** (0.36 – 1.08)	96 (89,98)	< 0.001
> 120 min	7	577	390	0.70* (0.08 – 1.32)	93 (71,98)	< 0.001
Type of Analyzer						
Sysmex	14	1557	2727	0.64*** (0.28 – 1.01)	95 (89,98)	< 0.001
Coulter	6	432	347	0.58* (0.08 – 1.08)	90 (61,98)	< 0.001
Advia	1	166	311	0.00 (− 0.19 – 0.19)	-	-
Not reported	6	328	276	0.48 (− 0.02 – 0.97)	88 (69,98)	< 0.001
Type of infarction						
Ischemic	25	2444	3405	0.57*** (0.31 – 0.83)	94 (89,97)	< 0.001
Hemorrhagic	3	239	286	0.07 (− 0.10 – 0.25)	0 (0,93)	0.6399

Table 10. Random Effect Model Subgroup Analysis for Mean Platelet Volume. *, P < 0.05; **, P < 0.01; ***, P < 0.001

15. Results of NLR-LMR study

15.1. Baseline Characteristics of Enrolled Patient

Throughout duration of our study, a total of 285 consecutive patients experiencing AIS and receiving intravenous thrombolysis were included in the research. The baseline characteristics of the enrolled patients can be found in Table 11. The average age of these patients was 66 years with a standard deviation of 12.9 years, and 44.2% of them were female. Their baseline NIHSS score had a median value of 6, with an interquartile range (IQR) between 5 and 9.1. The median mRS score at 90 days was 1.0.

Patients who had a poor outcome (mRS ≥ 2) at 90 days post-stroke tended to be older, had higher blood pressure levels, and had a higher incidence of atrial fibrillation. They also presented with more severe neurological deficits at admission compared to those who achieved a favorable outcome. Additionally, patients with poor outcomes exhibited significantly higher

NLR and considerably lower LMR in comparison to those with favorable outcomes, as demonstrated in Table 11.

	All Patients ***n*** **= 285**	**Good outcome (mRS=0-1)** ***n*** **= 190**	**Poor outcome (mRS=2-6)** ***n*** **= 95**	***p*** **value**
Demographic characteristics				
Age (year)	66 ± 12.9	62.8 ± 12.9	72.0 ± 10.2	< 0.001
Gender, male (%)	159 (55.8)	107 (56.3)	52 (54.7)	0.802
BMI (kg/m^2)	28.5 ± 5.9	28.5 ± 5.6	28.4 ± 6.5	0.900
Baseline laboratory results				
hsCRP (g/L)	2.8 (1.4-6.0)	2.5 (1.3-5.2)	3.5 (1.7-7.7)	0.060
White blood cell count (G/L)	8.1 (6.5-9.9)	8.04 (6.45-9.59)	8.15 (6.48-10.33)	0.455
Neutrophil count (G/L)	5.2 (4.0-7.1)	5.12 (3.99-6.86)	5.62 (4.17-7.55)	0.157
Lymphocyte count (G/L)	1.7 (1.2-2.3)	1.77 (1.31-2.3)	1.61 (1.15-2.24)	0.053
Monocyte count (G/L)	0.56 (0.44-0.69)	0.54 (0.43-0.69)	0.58 (0.47-0.71)	0.164
NLR	2.9 (1.94-4.82)	2.72 (1.86-4.66)	3.18 (2.17-5.94)	0.036
LMR	3.22 (2.42-4.29)	3.41 (2.51-4.55)	2.97 (1.87-3.92)	0.005
Vascular risk factors				
Smoking, No. (%)				
Non-smoker	204 (71.6)	131 (68.8)	73 (76.8)	0.152
Previous smoker	2 (0.7)	2 (1.1)	0	
Current smoker	79 (27.7)	57 (30.2)	22 (23.2)	
Previous stroke/TIA, No. (%)	67 (23.5)	38 (20)	29 (30.5)	0.055
Atrial fibrillation, No. (%)	29 (10.2)	14 (7.4)	15 (15.8)	0.026
PAD, No. (%)	9 (3.2)	6 (3.2)	3 (3.2)	1.000
Hyperlipidemia, No. (%)	181 (63.5)	123 (64.7)	58 (61.0)	0.602
DM, No. (%)	71 (24.9)	41 (21.6)	30 (31.6)	0.081
Hypertension, No. (%)	246 (86.3)	158 (83.2)	88 (92.6)	0.029
Therapy at stroke onset, No. (%)				
ACE inhibitor	148 (51.9)	92 (48.4)	56 (58.9)	0.103
Diuretic	118 (41.4)	71 (37.4)	48 (50.5)	0.056
Beta blocker	97 (34)	62 (32.6)	35 (36.8)	0.509
Calcium channel blocker	69 (24.2)	46 (24.2)	23 (24.2)	1.000
Alfa blocker	23 (8.1)	14 (7.4)	9 (9.5)	0.645
Hypertension therapy	189 (66.3)	121 (63.7)	68 (71.6)	0.231
Acetylsalicylic acid	86 (30.2)	52 (27.4)	34 (35.8)	0.171
Clopidogrel	23 (8.1)	16 (8.4)	7 (7.4)	0.822
Anticoagulant therapy, No. (%)				
Vitamin K antagonist	9 (3.2)	5 (2.6)	4 (4.2)	
Direct thrombin inhibitor	1 (0.4)	1 (0.5)	0	
Direct factor Xa inhibitor	0	0	0	
Low molecular weight heparin	3 (1.1)	2 (1.1)	1 (1.1)	

	All Patients n = 285	Good outcome (mRS=0-1) n = 190	Poor outcome (mRS=2-6) n = 95	*p* value
Lipid lowering therapy, No. (%)	78 (25)	44 (23.3)	27 (28.4)	0.384
Antidiabetic therapy, No. (%)	52 (17)	27 (14.2)	21 (22.1)	0.094
Stroke severity, No. (%)				
NIHSS at day 1				
0-5	110 (38.7)	93 (48.9)	17 (18.1)	< 0.001
6-10	98 (34.5)	65 (34.2)	33 (35.1)	
11-15	50 (17.6)	24 (12.6)	26 (27.7)	
>15	26 (9.2)	8 (4.2)	18 (19.1)	
NIHSS at day 7				
0-5	129 (46.9)	109 (57.7)	20 (23.3)	< 0.001
6-10	113 (41.1)	77 (40.7)	36 (41.9)	
11-15	24 (8.7)	3 (1.6)	21 (24.4)	
>15	9 (3.3)	0	9 (10.5)	
Hemorrhagic transformation				
aSICH, No. (%)	13 (4.6)	4 (2.1)	9 (9.5)	0.110
SICH, No. (%)	7 (2.5)	0	7 (7.4)	
Stroke localization				
ICA, No. (%)	193 (67.7)	112 (58.9)	81 (85.3)	< 0.001
VB, No. (%)	92 (32.3)	78 (41.1)	14 (14.7)	
Stroke etiology (TOAST)				
Large-artery atherosclerosis, No. (%)	62 (21.8)	55 (28.9)	7 (7.4)	< 0.001
Small-vessel occlusion, No. (%)	103 (36.1)	59 (31.1)	44 (46.3)	
Cardioembolic, No. (%)	23 (8.1)	17 (8.9)	6 (6.3)	
Other/undetermined, No. (%)	97 (34)	59 (31.1)	38 (40)	

Table 11. Baseline characteristics of enrolled patients according to long term outcomes (modified Rankin Scale at 90 days post event). Results are depicted as mean ± SD or median (interquartile range). ACE angiotensin converting enzyme, BA basilar artery, BMI body mass index, DM diabetes mellitus, hsCRP high sensitivity C reactive protein measurement, ICA internal carotid artery, LMR lymphocyte-monocyte ratio, mRS modified Rankin Scale, NIHSS National Institutes of Health Stroke Scale, NLR neutrophil-lymphocyte ratio, PAD peripheral artery disease, SICH symptomatic intracerebral hemorrhage, aSICH asymptomatic intracerebral hemorrhage, TIA transient ischemic attack, TOAST Trial of ORG 10172 in Acute Stroke Treatment, WBC white blood cell count

15.2. White Blood Cell Counts, NLR and LMR during Thrombolysis

Within the entire cohort, it was observed that 24 hours after thrombolysis, the median counts of neutrophils and monocytes, as well as the NLR, had all increased, while the median LMR had decreased when compared to the admission results (as detailed in Table 12). We identified a modest inverse correlation between neutrophil count and lymphocyte count at admission (r =

-0.166, p = 0.002) and on day 1 (r = -0.200, p = 0.001). Moreover, a significant yet modest positive correlation was identified between lymphocyte counts and monocyte counts at admission (r = 0.261, p< 0.001), though this correlation was not evident on day 1. Furthermore, neutrophil counts exhibited a correlation with monocyte counts both at admission (r = 0.381, p< 0.001) and on day 1 (r = 0.598, p< 0.001).

	Before thrombolysis	**24h after thrombolysis**	***p* Value**
Neutrophil (G/L)	5.24 (4.04-7.14)	6.26 (4.7-8.3)	< 0.001
Lymphocyte (G/L)	1.74 (1.25-2.3)	1.69 (1.28-2.15)	0.061
Monocyte (G/L)	0.56 (0.44-0.69)	0.66 (0.53-0.83)	< 0.001
NLR	2.9 (1.94-4.82)	3.58 (2.48-5.6)	< 0.001
LMR	3.22 (2.42-4.29)	2.58 (1.74-3.56)	< 0.001

Table 12. Median (interquartile range) leukocyte counts and ratios in acute ischemic stroke patients before and 24hours after thrombolysis. Neutrophil-lymphocyte ratio (NLR), lymphocyte- monocyte ratio (LMR); statistics: Wilcoxon Signed Rank test.

The results are presented as either mean with standard deviation (SD) or median along with the interquartile range. None of the leukocyte indices demonstrated an association with stroke etiology, stroke severity upon admission, or hemorrhagic transformation at admission, as detailed in Table 13 and Table 14. Conversely, the monocyte, neutrophil count, and NLR exhibited significant increases, whereas the LMR and lymphocyte count showed notable decreases 24 hours post-rtPA treatment in patients with more severe stroke.

A comparable trend was noted in individuals who encountered intracerebral hemorrhage associated with therapy, as indicated in Table 13.

	Time of blood sampling	Neutrophil (G/L)	Lymphocyte (G/L)	Monocyte (G/L)	NLR	LMR
Hemorrhagic transformation according to ECASS II (24h post-lysis)						
At admission						
	No hemorrhage (n = 264)	5.2 (4.1-7.1)	1.7 (1.2-2.3)	0.56 (0.44-0.70)	2.88 (1.93-4.82)	3.22 (2.42-4.30)
	aSICH (n = 13)	5.3 (3.8-7.2)	1.7 (1.3-1.9)	0.45 (0.39-0.58)	3.07 (2.32-6.50)	3.82 (2.68-5.10)
	SICH (n = 7)	6.2 (3.6-8.0)	1.8 (1.4-2.2)	0.60 (0.53-0.68)	3.41 (1.96-4.54)	2.97 (2.56-3.91)
	p Value	0.987	0.688	0.152	0.805	0.551
24h after thrombolysis						
	No hemorrhage (n = 264)	6.1 (4.6-8.2)	1.7 (1.3-2.2)	0.66 (0.52-0.83)	3.44 (2.45-5.20)	2.63 (1.75-3.59)
	aSICH (n = 13)	8.2 (6.6-9.1)	1.3 (1.1-1.9)	0.69 (0.62-0.87)	5.63 (3.31-8.58)	2.07 (1.2-2.59)
	SICH (n = 7)	9.7 (7.3-15.4)	1.3 (0.8-2.2)	0.91 (0.80-1.17)	7.12 (4.15-19.74)	1.51 (0.8-2.04)
	p Value	0.002	0.091	0.030	0.002	0.005
Stroke severity at admission						
At admission						
	NIHSS 0-5 (n = 110)	5.1 (4.0-7.0)	1.8 (1.4-2.4)	0.57 (0.44-0.71)	2.75 (1.81-3.98)	3.45 (2.51-4.51)
	NIHSS 6-10 (n = 97)	5.5 (4.4-6.8)	1.7 (1.2-2.3)	0.57 (0.45-0.70)	2.78 (2.00-4.95)	3.01 (2.33-4.34)
	NIHSS 11-16 (n = 50)	5.1 (4.0-7.5)	1.6 (1.2-2.1)	0.53 (0.42-0.66)	2.99 (2.08-6.56)	3.11 (2.41-4.13)
	NIHSS >16 (n = 26)	5.3 (3.6-6.9)	1.6 (1.1-1.9)	0.55 (0.44-0.63)	3.27 (2.10-5.73)	3.04 (2.36-4.06)
	p Value	0.782	0.067	0.581	0.330	0.441
24h after thrombolysis						
	NIHSS 0-5 (n = 110)	5.4 (4.3-7.5)	1.8 (1.4-2.4)	0.61 (0.49-0.79)	3.08 (2.10-4.47)	2.95 (2.27-3.92)
	NIHSS 6-10 (n = 97)	6.4 (4.7-8.0)	1.7 (1.4-2.2)	0.66 (0.56-0.82)	3.30 (2.48-5.17)	2.54 (1.85-3.59)
	NIHSS 11-16 (n = 50)	7.7 (5.0-9.7)	1.4 (1.2-2.0)	0.67 (0.56-0.85)	4.66 (3.04-6.85)	2.26 (1.67-2.87)
	NIHSS >16 (n = 26)	9.7 (7.2-13.4)	1.2 (0.9-1.7)	0.83 (0.68-1.08)	8.42 (4.05-12.98)	1.34 (1.04-1.87)
	p Value	< 0.001	< 0.001	0.004	< 0.001	< 0.001

Table 13. Leukocyte counts and ratios at admission and 24h after thrombolysis according to stroke severity at admission and thrombolysis safety. Data depicted as median (inter-quartile range). NLR neutrophil- lymphocyte ratio, LMR lymphocyte- monocyte ratio, aSICH asymptomatic intracerebral hemorrhage, SICH symptomatic intracerebral hemorrhage, ECASS II European Co-operative Acute Stroke Study-II, NIHSS National Institutes of Health Stroke Scale. Statistics: Kruskal-Wallis.

Stroke etiology (TOAST)	Neutrophil (G/L)	Lymphocyte (G/L)	Monocyte (G/L)	NLR	LMR
Large-artery atherosclerosis (n = 62)	4.9 (4.1-6.7)	1.8 (1.5-2.3)	0.57 (0.42-0.70)	2.68 (1.81-3.56)	3.56 (2.79-4.34)
Small-vessel occlusion (n = 103)	5.4 (3.8-7.4)	1.7 (1.2-2.3)	0.53 (0.43-0.71)	3.00 (1.95-5.03)	3.20 (2.31-4.42)
Cardioembolic (n = 23)	4.9 (3.9-6.7)	1.7 (1.3-1.9)	0.49 (0.40-0.65)	2.89 (2.10-4.26)	2.97 (2.63-4.24)
Other/undetermined (n = 97)	5.4 (4.2-7.2)	1.7 (1.2-2.3)	0.58 (0.47-0.68)	3.12 (1.94-5.52)	3.05 (2.36-4.04)
p Value	0.623	0.392	0.635	0.392	0.409

Table 14. Leukocyte counts and ratios at admission according to stroke etiology. Data are depicted a medium (interquartile range) NLR, neutrophil- lymphocyte ratio; LMR; lymphocyte-monocyte ratio; TOAST; TrialofORG10172 IN Acute stroke. Statistics: Kruskal-Wallis.

In contrast, the ASPECTS 10-8 group exhibited notably lower neutrophil counts and NLR values when compared to the ASPECTS 7 group on day 1, (Table 15). Univariate logistic regression analysis unveiled a considerable protective effect of elevated LMR at admission in relation to functional dependence at the 3-month mark following the event (OR = 0.755, 95% CI: 0.631, 0.903, p = 0.002), as elucidated in Table 16. However, this analysis did not reveal any discernible link between NLR and long-term functional outcomes. Furthermore, alongside LMR, elements such as age, hypertension, atrial fibrillation, and various stroke characteristics (including NIHSS, hemorrhagic transformation, and stroke localization) exhibited associations with the long-term outcome of therapy. Yet, within the multivariate model, only age, NIHSS, hemorrhagic transformation, and stroke localization emerged as the significant contributing factors, as succinctly presented in Table 17.

Table 15. Leukocyte counts and ratios according to ASPECTS at admission and 24h after thrombolysis. Data depicted as median (inter-quartile range). NLR: neutrophil-lymphocyte ratio. LMR: lymphocyte-monocyte ratio. Statistics: Mann-Whitney U test.

	Groups	Neutrophil (G/L)	Lymphocyte (G/)	Monocyte (G/L)	NLR	LMR
At admission	ASPECTS 10-8 (n = 5)	5.3 (4.1-6.9)	1.8 (1.3-2.3)	0.56 (0.45-0.69)	2.87 (1.83-4.95)	3.23 (2.41-4.23)
	ASPECTS 7-0 (n = 151)	6.3 (6.2-6.4)	1.6 (1.3-1.8)	0.64 (0.58-0.69)	3.41 (3.18-4.78)	2.56 (1.9-2.78)
p Value		0.193	0.740	0.270	0.271	0.298
At day 1	ASPECTS 10-8 (n = 38)	6.9 (4.9-8.3)	1.6 (1.3-2.1)	0.68 (0.53-0.89)	3.8 (2.55-6.04)	2.56 (1.62-3.47)
	ASPECTS 7-0 (n = 116)	8.5 (6.4-10.3)	1.5 (1.0-1.9)	0.74 (0.61-0.92)	5.59 (3.13-9.26)	2.01 (1.26-2.94)
p Value		0.002	0.132	0.218	0.004	0.072

Table 16. Univariable and multivariable logistic regression analyses depicting the associations of admission NLR, LMR and other baseline characteristics with functional dependence (mRS≥2) at 3 months post-event. LMR: lymphocyte-monocyte ratio. mRS: modified Rankin Scale. NIHSS: National Institutes of Health Stroke Scale. NLR: neutrophil-lymphocyte ratio.

Parameters	Univariable Logistic Regression Analysis		Multivariable Logistic Regression Analysis	
	OR (95%CI)	*p* Value	OR (95%CI)	*p* Value
Age (year)	1.076 (1.048-1.105)	0.001	1.052 (1.010-1-096)	0.015
NLR	1.046 (0.988-1.108)	0.121	1.044 (0.894-1.219)	0.584
LMR	0.755 (0.631-0.903)	0.002	0.534 (0.244-1.166)	0.115
Atrial fibrillation *n* (%)	1.656 (1.086-2.527)	0.019	0.503 (0.233-1.085)	0.080
Hypertension *n* (%)	2.546 (1.079-6.007)	0.033	0.695 (0.168-2.879)	0.616
NIHSS at day 1	2.333 (1.757-3.098)	< 0.001	2.448 (1.537-3.898)	< 0.001
NIHSS at day 7	4.613 (2.949-7.215)	< 0.001	8.762 (4.346-17.668)	< 0.001
Hemorrhagic transformation	6.874 (2.441-19.357)	< 0.001	6.608 (1.334-32.747)	0.021
Stroke localization	0.248 (0.131-0.469)	< 0.001	0.333 (0.122-0.909)	0.032

Despite the univariate model highlighting a robust link between NLR and LMR, assessed 24 hours after rtPA therapy, and functional outcomes at the 3-month mark following the event, the multivariate logistic regression model, which considered all potential confounding factors,

showed no noteworthy correlation between these parameters and functional outcomes at 3 months, as outlined in Table 17.

Table 17. Univariable and multivariable logistic regression analyses depicting the associations of day 1 NLR, LMR and baseline characteristics with functional independence at 3 months post-event (mRS≥2). LMR: lymphocyte-monocyte ratio. mRS: modified Rankin Scale.

Parameters	Univariable Logistic Regression Analysis		Multivariable Logistic Regression Analysis	
	OR (95%CI)	***p* Value**	**OR (95%CI)**	***p* Value**
Age (year)	1.076 (1.048-1.105)	< 0.001	1.056 (1.011-1.111)	0.014
hsCRP (g/L)	1.011 (1.001-1.022)	0.038	1.005 (0.979-1.031)	0.722
NLR	1.417 (1.266-1.585)	< 0.001	1.416 (0.963-2.083)	0.077
LMR	0.453 (0.347-0.591)	< 0.001	0.311 (0.103-1.413)	0.056
Atrial fibrillation. No. (%)	1.656 (1.086-2.527)	0.019	0.347 (0.191-0.981)	0.033
Hypertension. No. (%)	2.546 (1.079-6.007)	0.033	0.541 (0.117-2.493)	0.430
NIHSS at day 1	2.333 (1.757-3.098)	< 0.001	0.925 (1.420-3.948)	0.177
NIHSS at day 7	4.613 (2.949-7.215)	< 0.001	1.537 (1.335-1.769)	< 0.001
Hemorrhagic transformation	6.874 (2.441-19.357)	< 0.001	4.102 (0.589-28.579)	0.154
Stroke localization	0.248 (0.131-0.469)	< 0.001	0.393 (0.137-1.131)	0.083

NIHSS: National Institutes of Health Stroke Scale. NLR: neutrophil-lymphocyte ratio.

Initially, the study population exhibited median values at baseline, with NLR at 2.9 (interquartile range, IQR: 1.94, 4.82) and LMR at 3.22 (IQR: 2.42, 4.29). The optimal thresholds for predicting unfavorable functional outcomes at the 3-month post-event mark, determined through ROC analysis by maximizing the Youden index, were set at 5.73 for NLR and 2.08 for LMR (refer to Figure 8). These optimal cutoff values at admission led to the classification of patients into four distinct groups: low NLR–high LMR, high NLR–high LMR, low NLR–low LMR, and high NLR–low LMR.

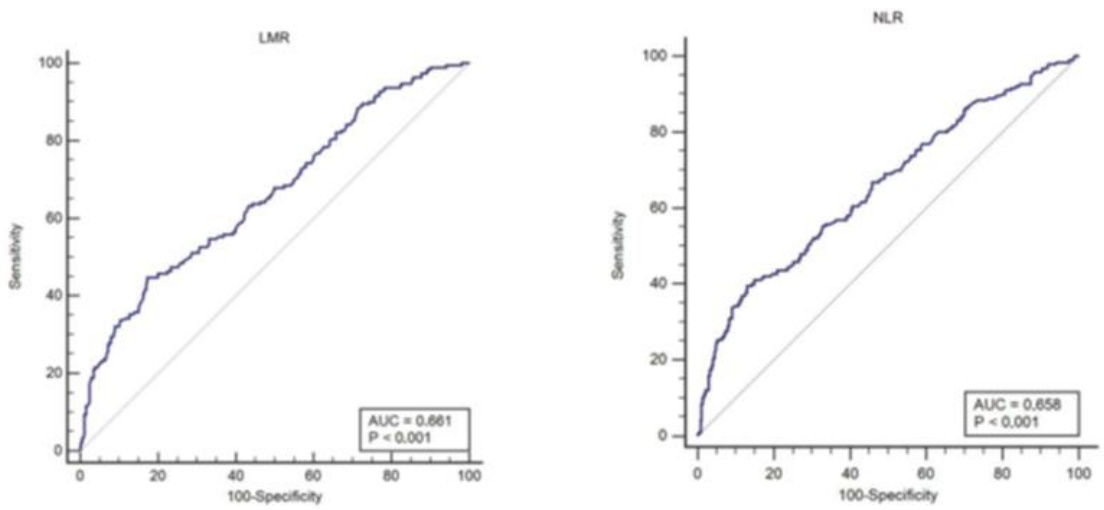


Figure 8. Receiver operating (ROC) curve analysis of admission neutrophil- to lymphocyte ratio (NLR) (a) and lymphocyte-to-monocyte ratio (LMR) (b) values predicting functional dependence (mRS2) at 3 months post- event.

Among the 190 patients who experienced favorable outcomes, a remarkable 77% found themselves in the low NLR–high LMR category at admission. In contrast, only 6.8% of patients were situated in the high NLR–low LMR group. These proportions saw little change by day 1, with 76% in the low NLR–high LMR category and 7.8% in the high NLR–low LMR category. On the other hand, within the 95-patient group with unfavorable outcomes, 67% belonged to the low NLR–high LMR category at admission, while a mere 21% were classified as high NLR–low LMR ($p = 0.001$) (see Figure 12). At the 24-hour mark following thrombolysis, the distribution among these groups underwent a significant transformation. Approximately 36% of patients were categorized as having low NLR–high LMR, whereas the high NLR–low LMR group accounted for 49% ($p< 0.001$) of patients (Figure 9).

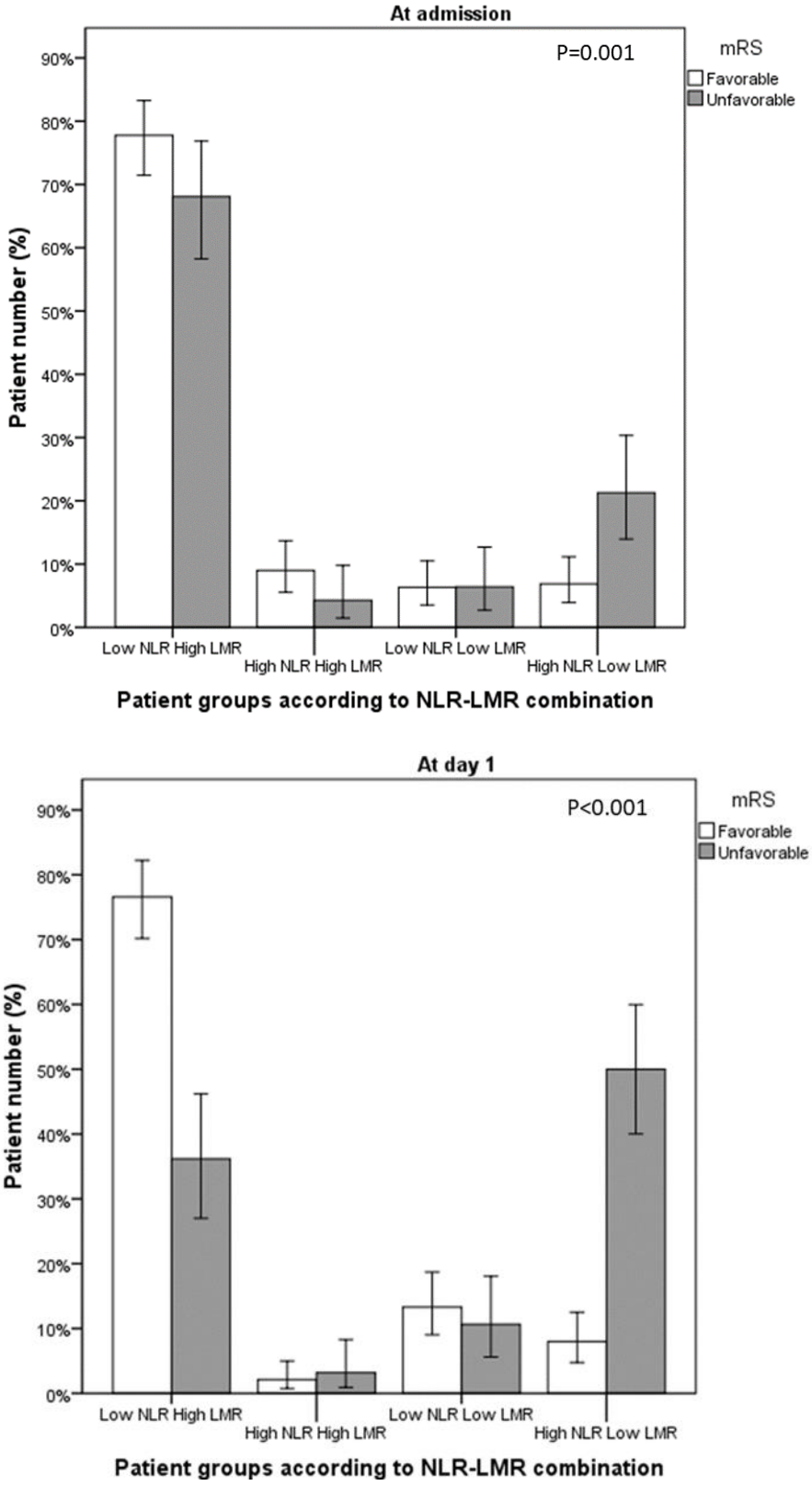


Figure 9. Proportion of patients in different NLR-LMR combination groups on admission and on day 1.

The joint evaluation of NLR and LMR at the 24-hour mark post-thrombolysis has been identified as identified predictor of adverse functional outcomes at 3 months post-event (OR = 3.407, 95% CI [1.449, 8.011], p = 0.005) for individuals categorized in the high NLR–low LMR group as opposed to those in the low NLR–high LMR group. This finding remains robust even when adjusting for all conceivable confounding variables (refer to Table 18).

Characteristics	Univariate Analysis, OR (95% CI)	*p* Value	Multivariate Analysis, OR (95% CI)[a]	*p* Value
At admission				
Low NLR-High LMR (n=211)	Ref	-	Ref	-
High NLR-High LMR n=22)	0.766 (0.310-1.891)	p = 0.563	0.338 (0.075-1.530)	p = 0.159
Low NLR-Low LMR (n=19)	0.993 (0.516-1.914)	p = 0.507	1.486 (0.462-4.779)	p = 0.507
High NLR-Low LMR (n=33)	5.496 (3.236-9.336)	p < 0.001	3.049 (1.205-7.714)	p = 0.019
At day 1				
Low NLR-High LMR (n=178)	Ref	-	Ref	-
High NLR-High LMR n=10)	1.412 (0.555-3.591)	p = 0.469	4.860 (0.816-28.944)	p = 0.082
Low NLR-Low LMR (n=35)	1.831 (0.914-3.671)	p = 0.088	1.168 (0.439-3.107)	p = 0.755
High NLR-Low LMR (n=62)	10.134 (5.685-18.066)	p < 0.001	6.353 (2.774-14.548)	p < 0.001

Table 18. Association of NLR-LMR combinations at admission and 24h after thrombolysis with poor functional outcome (mRS ≧2) at 3 months post-event. CI: confidence interval, OR: odds ratio, NLR: neutrophil-lymphocyte ratio, LMR: monocyte-lymphocyte ratio. A Controlled for: age, atrial fibrillation, hypertension, NIHSS, hemorrhagic transformation, and stroke localization.

16. Discussion

We undertook a comprehensive systematic review and meta-analysis of the existing literature to investigate PC and MPV in individuals with AS. Larger platelets, characterized by elevated MPV, are acknowledged to exhibit heightened metabolic and functional activity. Platelets with a high MPV possess greater stores of glycogen, ADP, ATP, and are more responsive to activating agents [151]. Defect in platelet activity has been associated with the occurrence of PICH [152]. Furthermore, platelets play a crucial role in thrombus formation, which can serve as the initiating events leading to stroke symptoms.

Recent meta-analyses have provided insights into elevated MPV in various pathological conditions [153, 154]. Conditions such as HT, DM, dyslipidemia, CAD, and smoking habits are established as important medical predispositions and comorbidities in the context of stroke. A growing body of evidence from existing literature has indicated a direct link between MPV and these conventional risk factors for cerebrovascular events [155-160]. For instance, among individuals with coronary artery disease, MPV was notably elevated (0.65 fL), and individuals with higher MPV displayed a 17% increased risk of experiencing cardiovascular events compared to those with lower MPV [161]. Furthermore, another meta-analysis revealed a significant elevation in MPV among individuals with acute MI compared to those without [162]. In our study, we found a substantial increase in MPV among acute ischemic stroke patients, along with a significant decrease in PC in both acute ischemic and hemorrhagic stroke cases.

Various authors have explored the potential role of MPV assessments as a promising biomarker for AS or a predictive tool for post-stroke patient outcomes [16, 149]. The association between MPV and stroke may be attributed to the heightened platelet activity, aggregation propensity, and rapid turnover observed in individuals with elevated MPV. Studies have indicated that increased MPV correlates with the presence of more hemostatically active platelets with a

heightened tendency to aggregate [163]. Furthermore, due to accelerated turnover of platelets bone marrow releases younger, more active, and larger platelets [164]. Our comprehensive analysis uncovered a statistically significant mean difference of 0.51 fL, signifying substantially higher MPV values in AS patients compared to controls. Furthermore, even after meticulous adjustments for the type of analyte or analyzer, MPV remained notably elevated in patients compared to controls. It's important to note that while these differences are statistically significant, they represent relatively minor changes in absolute terms. These findings likely reflect distinct characteristics of the platelet population and the prevalence of more responsive platelets within this patient group's bloodstream.

As platelets typically have a lifespan ranging from 8 to 10 days, the influence of heightened MPV on prothrombotic tendencies and the increased risk of stroke likely predates the onset of a stroke. Notably, stroke patients exhibited elevated platelet activation, as evidenced by increased CD62P (P-selectin) levels and the presence of circulating monocyte-platelet complexes [165]. Conversely, the levels of reticulated platelets, indicative of platelet production, mirrored those of controls among stroke patients [166]. These findings suggest an ongoing stimulation of platelet activation without excessive platelet production following a stroke. Continuous monitoring of stroke patients revealed persistent elevations in MPV even three to 6 months post-stroke [123, 126]. A limited number of studies concerning acute hemorrhagic stroke and hyporeactive platelets, characterized by significantly reduced platelet aggregation rates induced by ADP [167], may partially account for the sustained MPV levels in acute hemorrhagic stroke cases.

The decline in platelet count (PC) during the acute phase of ischemic stroke can be ascribed to heightened platelet consumption [31]. However, comprehending the underlying reasons for the reduced PC levels in patients with acute hemorrhagic stroke is a more intricate matter, in some cases, low platelet count before stroke might cause hemorrhagic stroke. It is improbable that

non-traumatic acute hemorrhagic strokes involve hemorrhages extensive enough to cause a significant depletion of platelets. Alternative factors, such as medications like antiepileptics or antibiotics, may have contributed to the observed decrease in PC. It becomes evident that modifying PC as an acute-phase marker requires a timeframe that exceeds the duration of acute stroke. Moreover, it is imperative to acknowledge that pre-analytical conditions play a pivotal role in the assessment of mean MPV. To regard MPV as a potential risk factor for acute stroke, standardizing its measurement emerges as an essential consideration. This necessity extends not only to laboratory protocols but also holds paramount significance for the clinical community in terms of accurate interpretation and clinical decision-making.

The selection of anticoagulants for blood samples exerts a substantial impact on the outcomes of platelet parameters when assessed through traditional hematology analyzers [168]. Existing evidence has substantiated that the introduction of EDTA as an anticoagulant within the sample may give rise to artificial platelet swelling [69]. This phenomenon is, in part, attributable to alterations in the platelet cell wall, modifications to the membranes lining the canalicular system, and shifts in the phosphorylation patterns of platelet proteins, all induced by exposure to EDTA [169, 170]. Intriguingly, among the studies encompassed in this meta-analysis, 61% opted for EDTA as the anticoagulant, a choice that correlated with markedly higher mean platelet volume (MPV) values for the patient cohort. It is worth noting that nearly half of the studies omitted any specification regarding the type of analyte employed in their investigations. Moreover, the type of anticoagulant utilized for blood samples can profoundly influence platelet count (PC) outcomes [171]. Notably, the use of citrate anticoagulant may incite the formation of minuscule platelet micro-aggregates. Our findings reveal that, when considering the patient cohort in its entirety versus the control group, the calculated pooled mean difference for PC was -0.30 G/L. Furthermore, it is paramount to acknowledge that hematology analyzers encompass varying methodologies for the measurement of platelet parameters. These

methodologies predominantly hinge on impedance or optical techniques, which, however, do not account for the morphological changes in platelets [173].

Consequently, these methodologies exhibit incongruities, and another pivotal parameter influencing MPV is the duration of sample storage [174]. Despite the fact that not all investigations documented the timeframe for sample preservation, it was ascertained that MPV demonstrated a significant elevation in comparison to the control group, whether the samples were stored for ≤120 minutes or >120 minutes. In order to enhance the uniformity of MPV reporting, it is recommended to standardize the interval between venipuncture and MPV assessment.

It is important to acknowledge the limitations of this study. The heterogeneity observed in the literature regarding the correlation between MPV and stroke is multifactorial. The meta-analysis revealed substantial heterogeneity, primarily arising from disparities in preanalytical factors and the demographic attributes of the study cohorts. Regrettably, these essential factors were often unreported, representing a potential wellspring of heterogeneity. Furthermore, only a restricted number of studies factored in the potential confounding influence of traditional cerebrovascular risk factors, and these studies displayed profound variations in preanalytical factors. As such, the results must be interpreted judiciously in light of the significant heterogeneity evident in certain studies. The variations in the timeframe between the onset of stroke and blood sampling, along with the lack of specificity in reporting the type of analyte or analyzer employed, may have contributed to the divergent findings. Additionally, the protracted contact between blood samples and anticoagulants can yield spurious results. The heterogeneity among the studies may also be partially attributed to the diversity in the analyte utilized for anticoagulation within the samples or the assay methods. Consequently, it is highly advisable that forthcoming research endeavors adhere to a standardized set of covariates and preanalytical factors. This standardization can be achieved by establishing a specific window

for the measurement of sample results, specifying the type of anticoagulant utilized in the sample tubes, and delineating the method of measurement. The absence of comprehensive documentation concerning patient-associated preanalytical factors has markedly contributed to the augmented variability among the studies.

In summary, the assessment of MPV as an integral facet of standard complete blood counts offers a readily accessible and potentially informative marker of platelet turnover. The findings from this investigation underscore the pivotal role of platelets in the pathogenesis of stroke. Both PC and MPV demonstrated statistically significant deviations in comparison to control populations. Remarkably, individuals afflicted with acute ischemic stroke displayed a substantial elevation in MPV. In contrast, patients with both acute ischemic and hemorrhagic strokes exhibited notably diminished PC counts. These distinctive attributes may bear significance in the etiology of stroke and its underlying pathophysiology. Crucially, this study stands as a pioneering endeavor, being the first to present and deliberate upon the evidence bolstering the combination of NLR and LMR, appraised at the 24-hour mark post-thrombolysis, as an autonomous prognostic factor bearing clinical import. This innovative approach not only demonstrates practical feasibility in identifying patients with acute ischemic stroke who face an unfavorable outcome at the 3-month juncture following intravenous thrombolysis but also holds its own as an independent prognostic factor. This standing was corroborated via a comprehensive multivariate analysis, further cementing the autonomy of high NLR–low LMR in prognosticating suboptimal outcomes at the 3-month threshold in patients with acute ischemic stroke post- rt-PA therapy. The predictive prowess of this model extends its reach to encompass other determinants, including gender, NIHSS scores, and TOAST classification.

Inflammation plays a pivotal role in the pathogenesis of ischemic brain injury. Following a stroke, ischemia triggers microglia activation, subsequently leading to the infiltration of blood-

derived immune cells into the brain tissue within hours to a few days [175, 176]. Neutrophils swiftly reach the infarcted area in the initial hours following brain infarction, monocytes arrive within the first 24 hours, and lymphocytes make their entrance between 24 and 48 hours [177-179]. This influx of immune cells results in the release of reactive oxygen species and a plethora of inflammatory mediators, adhesion molecules, cytokines, chemokines, and proteases, which collectively exacerbate tissue damage [180]. Experimental stroke models have revealed increased hematopoiesis and an augmented release of neutrophils from the bone marrow due to heightened stimulation of the autonomic nervous system post-stroke [181].

Studies have indicated that post-thrombolysis NLR serves as a marker for an elevated risk of poor outcomes within three months following the onset of a stroke, and similar findings have been reported by other research groups [182, 183]. Our results align with these studies, demonstrating no independent association between infarct size and NLR or LMR twenty-four hours post-stroke [184]. Pektezel et al. conducted a retrospective analysis of acute stroke patients treated with rtPA by comparing those with favorable outcomes (mRS score of 3) to those with excellent outcomes (mRS score of 0 or 1) at admission and after 24 hours [185]. Their study revealed a significant elevation in NLR from admission to 24 hours post-event, with an NLR value of 3.6 after 24 hours indicative of a favorable prognosis. They concluded that the elevated NLR during the first 24 hours is a secondary phenomenon associated with a poor prognosis. In contrast, a recent meta-analysis could not amass sufficient data to substantiate this assertion [186].

Shi et al. conducted a study in which they did not identify any statistically significant differences in NLR upon admission between patients who later exhibited favorable versus poor outcomes. Our investigation aligns with these findings, as we determined a similar NLR threshold (established at 5.73) and observed no significant disparities in NLR at the time of admission between individuals who experienced unfavorable and favorable outcomes [182].

Additionally, other researchers, although working with a relatively small patient cohort, did not discern any significant associations between NLR or the LMR and the long-term outcomes of patients with AIS treated with thrombolysis [187].

Beyond these considerations, it is noteworthy that monocytes assume a pivotal role in the inflammatory processes occurring within the cerebral infarct area resulting from cerebral ischemia and hypoxia. Monocytes release a spectrum of inflammatory mediators, encompassing chemokines, intercellular adhesion molecule-1, interleukin-1, IL-6, IL-8, and tumor necrosis factor, thereby actively contributing to the progression of inflammation. Furthermore, monocytes have a role in the promotion of thrombosis and vascular occlusion by forming aggregates in conjunction with platelets, thus amplifying the extent of ischemic injury [188].

Within the ischemic cerebral environment, monocyte-derived macrophages (MDMs) undergo differentiation from their precursor monocytes, as delineated in previous research [189]. These MDMs exhibit considerable phagocytic potency and play a pivotal role in the protracted and spontaneous functional recuperation of the brain following an ischemic insult [190].

Furthermore, the Lymphocyte-to-Monocyte Ratio (LMR) at the time of patient admission has also been a subject of investigation for its potential to prognosticate the clinical outcomes at the 3-month mark in stroke patients receiving thrombolysis therapy [191]. This analysis unveiled a crucial finding: a higher LMR value, with a defined cutoff point at 3.48, emerged as an independent determinant for forecasting the clinical outcomes of stroke patients, even prior to the administration of rt-PA.

Additionally, an examination into the temporal variations in the levels of peripherally circulating leukocytes revealed a striking phenomenon: an immediate post-ischemic stroke event is marked by an exponential decrease in the lymphocyte count [192]. This noteworthy

observation provides valuable insights into the dynamics of immune response following ischemic stroke.

Reduced lymphocyte counts, signifying severe brain damage, have shown predictive value for unfavorable neurological recovery and poor functional outcomes post-stroke [193]. Our analysis aligns with this trend, as it revealed a significant rise in the number of patients experiencing poor outcomes within the high NLR–low LMR group in the first 24 hours post-thrombolysis. This observation underscores the relative association between diminished lymphocyte counts and unfavorable outcomes.

One potential mechanistic explanation is that regulatory lymphocytes both B and T cells, characterized as shielding cells that curtail disease progression, promote immune homeostasis, and generate anti-inflammatory agents, witness an upsurge in brain tissue following ischemic injury [194]. Notably, this subdivision of WBCs regulates expression of sympathomimetic and parasympathetic mediated receptors on their cell surface. Lymphocytes display countless cholinergic receptors on their surfaces meanwhile lower number of receptors of sympathetic mediators, while granulocytes exhibit a reverse relation with receptors [195]. This dynamic interplay among leukocyte subsets may underlie the observed trends.

Our research, in line with previous findings, demonstrates that there is no substantial association between SICH, severity of stroke, and leukocyte indices measured at time of patient is admitted to hospital [184, 197, 198]. The association between WBC profiles and stroke outcomes after mechanical thrombectomy is the subject of some investigations [184, 199]. In a study, higher counts of neutrophils and NLR at admission and on day 1, as well as lower lymphocyte counts on day 1, were linked to poor prognosis (mRS > 2) [199]. In another study, higher NLR and lower LMR 24 hours after mechanical thrombectomy (but not at admission) were significant predictors of mRS at the 3-month functional outcome [184]. They established optimal cut-off values of 5.5 for NLR and 2.0 for LMR post-thrombectomy.

Our study is the first to delve into the value of the combined post-thrombolysis high NLR–low LMR ratio for assessing the prognosis of AIS patients at 3 months post-event. Our findings are supported by previous research, which indicated the limited reliability of the pre-thrombolysis prognostic value of NLR measurements [177]. Our results reveal that the NLR–LMR index, as determined 24 hours post-lysis, more accurately categorizes patients according to their 3-month outcomes, providing superior diagnostic accuracy. In summary, our investigation has unveiled that an elevated NLR-low LMR composite, evaluated 24 hours post-thrombolysis, stands as an autonomous prognosticator of unfavorable functional outcomes at the 3-month juncture subsequent to an ischemic episode. The remarkable increase in the representation of patients within the high NLR-low LMR category among those experiencing unfavorable outcomes conveys the potential of this combination to signify a less optimistic prognosis. However, when we isolate the assessment of NLR and LMR, no substantial correlations with extended-term outcomes manifest.

Our findings underscore the importance of incorporating MPV, PC, NLR, and LMR measurements, both individually and in combination, to enhance the precision of prognostic predictions in AIS patients. These parameters can be easily obtained through routine blood test, offering a easily accessible and cost-effective tool for healthcare providers. The identification of individuals at a higher risk of adverse outcomes can facilitate the customization and optimization of post-thrombolysis therapy, potentially leading to improved longstanding quality of life as well as a reduced liability of acute ischemic stroke. Further research is warranted to validate these findings and explore the underlying mechanisms that link NLR, LMR, platelet indices, and stroke.

17. Summary

Ischemic stroke is a leading cause of mortality and disability characterized by inflammation throughout all stages. Our investigation aimed to evaluate the predictive potential of platelet indices in AIS, and predictive value of NLR, and LMR in AIS patients undergoing intravenous rt-PA treatment. A systematic review and meta-analysis assessed the relationship between MPV and PC as AIS markers. 34 eligible studies comparing PC and MPV in AIS patients to controls were included, with subgroup analyses conducted to explore differences in platelet parameters. Additionally, prospective research involved 285 adult AIS patients receiving rt-PA within a 4.5-hour interval. NLR and LMR were calculated before and after thrombolysis, with blood samples collected upon admission and 24 hours post-thrombolysis. Clinical data, including NIHSS and mRS scores at 90 days, were gathered, along with investigation of therapy-related ICH.

Comprehensive analysis revealed significantly reduced PC and increased MPV in AIS patients compared to controls, with variations among stroke types and anticoagulant methods observed in subgroup studies. Prospective analysis showed no significant relationship between NLR or LMR within 90 days. However, high NLR combined with low LMR 24 hours post-thrombolysis independently predicted poor outcomes within 90 days, significantly impacting patient proportions in the poor outcome group. Platelet parameters, particularly PC and MPV, may serve as useful indicators of AIS, with variations noted depending on stroke type and blood collection methods. Moreover, the combination of NLR and LMR 24 hours post-thrombolysis emerged as a distinct predictor of poor 3-month functional outcomes in AIS patients, potentially enhancing prognostic estimations and treatment decisions following thrombolysis.

18. Key words

Acute ischemic stroke, acute hemorrhagic stroke, intravenous thrombolysis, atherosclerosis, cardiac thromboembolism, Mean platelet volume, meta-analysis, platelet count, platelet indices, Lymphocyte-Monocyte ratio, Neutrophil–lymphocyte ratio

19. References

[1] Feigin, V. L. et al, “Global, regional, and country-specific lifetime risks of stroke,” N. Engl. J.Med., vol. 379, p. 2429–2437, 2018.

[2] Sacco, R. L. et al., “An updated definition of stroke for the,” Stroke, vol. 44, p. 2064–2089, 2013.

[3] Astrup, J., Siesjo, B. K. & Symon, L., “Thresholds in cerebral ischemia—the ischemic penumbra.,” Stroke, vol. 12, p. 723–725, 1981.

[4] The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group., “Tissue plasminogen activator for acute ischemic stroke.,” N. Engl. J. Med., vol. 333, p. 1581–1587, 1955.

[5] Stroke Unit Trialists’ Collaboration., “Collaborative systematic review of the randomised trials of organised inpatient (stroke unit) care after stroke.,” BMJ, vol. 314, p. 1151–1159, 1977.

[6] Emberson, J. et al., “Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute Ischemic stroke: a meta-analysis of individual patient data from randomised trials,” Lancet, vol. 384, p. 1929–1935, 2014.

[7] Thomalla, G. et al., “MRI-guided thrombolysis for stroke with unknown time of onset.,” N. Engl. J. Med., vol. 379, p. 611–622, 2018.

[8] Ma, H. et al., “A multicentre, randomized, double blinded, placebo-controlled phase 3 study to investigate extending the time for thrombolysis in emergency neurological deficits (EXTEND).,” Int. J. Stroke, vol. 7, pp. 74-80, 2012.

[9] Campbell, B. C. V. et al., “Extending thrombolysis to 4.5-9 hours and wake-up stroke using perfusion imaging: a meta-analysis of individual patient data from EXTEND, ECASS4-EXTEND and EPITHET.,” Lancet, vol. 394, p. 139–147, 2019.

[10] Goyal, M. et al., “Endovascular thrombectomy after large-vessel Ischemic stroke: a meta-analysis of individual patient data from five randomised trials.,” Lancet, vol. 387, p. 1723–1731, 2016.

[11] Albers, G. W. et al., “Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging.,” N. Engl. J. Med., vol. 378, p. 708–718, 2018.

[12] Nogueira, R. G. et al., “Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct.,” N. Engl. J. Med., vol. 378, p. 11–21, 2018.

[13] Saver, J. L. et al., “Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: a meta-analysis.,” JAMA, vol. 316, p. 1279–1288, 2016.

[14] Global Burden of Disease Stroke Collaborators., “Global, regional, and national burden of stroke, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016.,” Lancet Neurol., vol. 18, p. 439–458, 2019.

[15] World Stroke Organization., WSO global stroke fact sheet., 2019.

[16] Global Burden of Disease Causes of Death Collaborators., “Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the global burden of disease study 2017.,” Lancet, vol. 392, p. 1736–1788, 2018.

[17] Feigin, V. L. et al., “Update on the global burden of ischemic and hemorrhagic stroke in 1990-2013: the GBD 2013 study.,” Neuroepidemiology, vol. 45, p. 161–176, 2015.

[18] Krishnamurthi, R. V. et al., “Global and regional burden of first-ever Ischemic and haemorrhagic stroke during 1990-2010: findings from the global burden of disease study 2010.,” Lancet Glob. Health, vol. 1, p. e259–e281, 2013.

[19] Krishnamurthi, R. V. et al., “Stroke prevalence, mortality and disability-adjusted life years in adults aged 20-64 years in 1990-2013: data from the global burden of disease 2013 study.,” Neuroepidemiology, vol. 45, p. 190–202, 2015.

[20] Feigin, V. L., Norrving, B. & Mensah, G., “A. Global burden of stroke.,” Circ. Res, vol. 120, p. 439–448, 2017.

[21] Bevan, S. et al., “Genetic heritability of ischemic stroke and the contribution of previously reported candidate gene and genome-wide associations.,” Stroke, vol. 43, p. 3161–3167, 2012.

[22] O’Donnell, M. J. et al., “Risk factors for Ischemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study.,” Lancet, vol. 376, p. 112–123, 2010.

[23] Bang, O. Y., Ovbiagele, B. & Kim, J. S., “Nontraditional risk factors for ischemic stroke: an update.,” Stroke, vol. 46, p. 3571–3578 , 2015.

[24] Shah, A. S. et al., “Short term exposure to air pollution and stroke: systematic review and meta-analysis.,” BMJ, vol. 350, p. h1295, 2015.

[25] Bruce C. V. Campbell, Deidre A. De Silva, Malcolm R. Macleod, Shelagh B. Coutts,Lee H. Schwamm, Stephen M. Davis and Geoffrey A. Donnan , “Ischemic stroke,” Nature Reviews Disease Primers, 2019.

[26] Shaaban, A. M. & Duerinckx, A. J., “Wall shear stress and early atherosclerosis: a review.,” AJR Am. J. Roentgenol., vol. 174, p. 657–1665, 2000.

[27] Jia, B. et al., “Mechanical thrombectomy and rescue therapy for intracranial large artery occlusion with underlying atherosclerosis.,” J. Neurointerv.Surg., vol. 10, p. 746–750, 2018.

[28] Kim, J. S., Kim, Y. J., Ahn, S. H. & Kim, B. J., “Location of cerebral atherosclerosis: why is there a difference between East and West?” Int. J. Stroke, vol. 13, p. 35–46, 2018.

[29] Holmstedt, C. A., Turan, T. N. & Chimowitz, M. I., “Atherosclerotic intracranial arterial stenosis: risk factors, diagnosis, and treatment.,” Lancet Neurol., vol. 12, p. 1106–1114, 2013.

[30] Hao, Y. et al., “Predictors for symptomatic intracranial hemorrhage after endovascular treatment of acute ischemic stroke.,” Stroke, vol. 48, p. 1203–1209, 2017.

[31] Link, M. S. et al., “Stroke and mortality risk in patients with various patterns of atrial fibrillation: results from the ENGAGE AF-TIMI 48 trial (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48,”). Circ. Arrhythm. Electrophysiol., vol. 10, p. e004267, 2017.

[32] Morillo, C. A., Banerjee, A., Perel, P., Wood, D. & Jouven, X., “Atrial fibrillation: the current epidemic.,” J. Geriatr. Cardiol., vol. 14, p. 195–203, 2017.

[33] Lau, D. H., Nattel, S., Kalman, J. M. & Sanders, P., “Modifiable risk factors and atrial fibrillation,” Circulation, vol. 136, p. 583–596, 2017.

[34] Kirchhof, P. et al., “2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS.,” Eur. Heart J., vol. 37, p. 2893–2962, 2016.

[35] Hagen, P. T., Scholz, D. G. & Edwards, W. D., “Incidence and size of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts.,” Mayo Clin. Proc., vol. 59, p. 17–20, 1984.

[36] . Mas, J. L. et al., “Patent foramen ovale closure or anticoagulation vs. antiplatelets after stroke.,” N. Engl. J. Med., vol. 377, p. 1011–1021, 2017.

[37] Saver, J. L. et al., “Long-term outcomes of patent foramen ovale closure or medical therapy after stroke.,” N. Engl. J. Med., vol. 377, p. 1022–1032, 2017.

[38] Sondergaard, L. et al., “Patent foramen ovale closure or antiplatelet therapy for cryptogenic stroke.,” N. Engl. J. Med., vol. 377, p. 1033–1042, 2017.

[39] Arboix, A., Jimenez, C., Massons, J., Parra, O. & Besses, C., “Hematological disorders: a commonly unrecognized cause of acute stroke.,” Expert Rev.Hematol., vol. 9, p. 891–901, 2016.

[40] Switzer, J. A., Hess, D. C., Nichols, F. T. & Adams, R. J., “Pathophysiology and treatment of stroke in sickle-cell disease: present and future.,” Lancet Neurol., vol. 5, p. 501–512, 2006.

[41] Bal, S. et al., “Time dependence of reliability of noncontrast computed tomography in comparison to computed tomography angiography source image in acute ischemic stroke.,” Int. J. Stroke, vol. 10, p. 55–60, 2015.

[42] Roman, L. S. et al., “Imaging features and safety and efficacy of endovascular stroke treatment: a meta-analysis of individual patient-level data.,” Lancet Neurol., vol. 17, p. 895–904, 2018.

[43] Hjort, N. et al., “Ischemic injury detected by diffusion imaging 11 minutes after stroke.,” Ann. Neurol., vol. 58, p. 462–465, 2005.

[44] Campbell, B. C. V. et al., “The infarct core is well represented by the acute diffusion lesion: sustained reversal is infrequent.,” J. Cereb. Blood Flow Metab., vol. 32, pp. 50-56, 2012.

[45] Simard, J. M., Kent, T. A., Chen, M., Tarasov, K. V. & Gerzanich, V., “Brain oedema in focal ischaemia: molecular pathophysiology and theoretical implications.,” Lancet Neurol., vol. 6, p. 258–268, 2007.

[46] CAST (Chinese Acute Stroke Trial) Collaborative Group., “CAST: randomised placebo-controlled trial of early aspirin uses in 20,000 patients with acute Ischemic stroke.,” Lancet, vol. 349, p. 1641–1649, 1977.

[47] International Stroke Trial Collaborative Group., “The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute Ischemic stroke.,” Lancet, vol. 349, p. 1569–1581, 1977.

[48] Sacco, R. L. et al., “Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke.,” N. Engl. J. Med, vol. 359, p. 1238–1251, 2008.

[49] Johnston, S. C. et al., “Clopidogrel and aspirin in acute ischemic stroke and high-risk TIA,” N. Engl. J. Med., vol. 379, p. 215–225, 2018.

[50] Johnston, S. C. et al., “Time course for benefit and risk of clopidogrel and aspirin after acute transient ischemic attack and minor ischemic stroke.,” Circulation, vol. 140, p. 658–664, 2019.

[51] Hacke, W. et al., “Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS).,” JAMA, vol. 274, p. 1017–1025, 1995.

[52] Hacke, W. et al., “Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute Ischemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators.,” Lancet, vol. 352, p. 1245–1251, 1998.

[53] Albers, G. W., Clark, W. M., Madden, K. P. & Hamilton, S. A., “ATLANTIS trial: results for patients treated within 3 hours of stroke onset. Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke.,” Stroke, vol. 33, p. 493–495, 2002.

[54] Clark, W. M. et al., “Recombinant tissue-type plasminogen activator (alteplase) for ischemic stroke 3 to 5 hours after symptom onset. The Atlantis study: a randomized controlled trial. alteplase thrombolysis for acute noninterventional therapy in ischemic stroke.,” JAMA, vol. 282, p. 2019–2026, 1999.

[55] Sandercock, P. et al., “The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute Ischemic stroke (the Third International Stroke Trial [IST-3]): a randomised controlled trial.,” Lancet, vol. 379, p. 2352–2363, 2012.

[56] Lees, K. R. et al., “Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials.,” Lancet, vol. 375, p. 1695–1703, 2010.

[57] Muchada, M. et al., “Impact of time to treatment on tissue-type plasminogen activator-induced recanalization in acute ischemic stroke.,” Stroke, vol. 45, p. 2734–2738, 2014.

[58] Powers, W. J. et al., “2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association.,” Stroke, vol. 49, p. e46–e110, 2018.

[59] Linke, Y. Schreiber, B. Picard-Willems et al., “Activated platelets induce an anti-inflammatory response of monocytes/ macrophages through cross-regulation of PGE2 and cytokines.,” Mediators of Inflammation., vol. 2017, pp. 16, 14, 2017.

[60] Aleksandra Korniluk, Olga Martyna Koper-Lenkiewicz, Joanna Kamińska, Halina Kemona, and Violetta Dymicka-Piekarska., “Mean Platelet Volume (MPV): New Perspectives for an Old Marker in the Course and Prognosis of Inflammatory Conditions.,” Mediators of Inflammation, vol. 2019, p. 14, 2019.

[61] K. R. Machlus and J. E. Italiano Jr., “The incredible journey: from megakaryocyte development to platelet formation.,” The Journal of Cell Biology, vol. 201, p. 785–796, 2013.

[62] J. Zimmet and K. Ravid., “Polyploidy: occurrence in nature, mechanisms, and significance for the megakaryocyteplatelet system.,” Experimental Hematology, vol. 28, no. 1, p. 3–16, 2000.

[63] S. R. Patel, J. H. Hartwig, and Italiano JE Jr., “The biogenesis of platelets from megakaryocyte proplatelets.,” Journal of Clinical Investigation., vol. 115, no. 12, p. 3348–3354, 2005.

[64] J. N. Thon, H. Macleod, A. J. Begonja et al., “Microtubule and cortical forces determine platelet size during vascular platelet production.,” Nature Communications., vol. 3, no. 1, 2012.

[65] K. Kaushansky., “The molecular mechanisms that control thrombopoiesis.,” Journal of Clinical Investigation, vol. 115, no. 12, p. 3339–3347, 2005.

[66] A. Y. Gasparyan, L. Ayvazyan, D. P. Mikhailidis, and G. D.Kitas, “Mean platelet volume: a link between thrombosis and inflammation?,” Current Pharmaceutical Design, vol. 17, no. 1, p. 47–58, 2011.

[67] O. Behnke and A. Forer., “From megakaryocytes to platelets: platelet morphogenesis takes place in the bloodstream.,” European Journal of Haematology., vol. 61, p. 3–23, 1998.

[68] J. Hartwig and J. Italiano., “The birth of the platelet.,” Journal of Thrombosis and Haemostasis., vol. 1, no. 7, pp. 1580-1586, 2003.

[69] M. R. Barnard, L. A. Krueger, A. L. Frelinger III, M. I. Furman, and A. D. Michelson., “Whole blood analysis of leukocyte-platelet aggregates.,” Current Protocols in Cytometry, 2003.

[70] Y. U. Budak, M. Polat, and K. Huysal, “The use of platelet indices, plateletcrit, mean platelet volume and platelet distribution width in emergency non-traumatic abdominal surgery: a systematic review,” Biochemical Medicine, vol. 26, no. 2, p. 178–193, 2016.

[71] J. Sikora and B. Kostka, “Blood platelets as pharmacological model,” Postępy Biologii Komórki, vol. 3, no. 32, p. 561– 569, 2005.

[72] C. B. Thompson and J. A. Jakubowski, “The pathophysiology and clinical relevance of platelet heterogeneity,” Blood, vol. 72, no. 1, pp. 1-8, 1988.

[73] A. Panasiuk, “Płytki krwi w przewlekłych chorobach wątroby, “Medical Science Review,” Hepatologia,, vol. 11, pp. 83-86, 2011.

[74] P. Ntolios, N. Papanas, E. Nena et al., “Mean platelet volume as a surrogate marker for platelet activation in patients with idiopathic pulmonary fibrosis,” Clinical and Applied Thrombosis/Hemostasis, vol. 22, no. 4, pp. 346-350, 2015.

[75] S. A. Burstein, T. Downs, P. Friese et al., “Thrombocytopoiesis in normal and sublethally irradiated dogs: response to human interleukin-6,” Blood, vol. 80, no. 2, pp. 420-428, 1992.

[76] S. K. Braekkan, E. B. Mathiesen, I. Njolstad, T. Wilsgaard, J. Stormer, and J. B. Hansen., “Mean platelet volume is a risk factor for venous thromboembolism: the Tromsø study.,” Journal of Thrombosis and Haemostasis, vol. 8, no. 1, p. 157–162, 2010.

[77] S. G. Chu, R. C. Becker, P. B. Berger et al., “Mean platelet volume as a predictor of cardiovascular risk: a systematic review and meta-analysis.,” Journal of Thrombosis and Haemostasis., vol. 8, no. 1, p. 148–156, 2010.

[78] E. Y. Senchenkova, S. Komoto, J. Russell et al., “Interleukin-6 mediates the platelet abnormalities and thrombogenesis associated with experimental colitis.,” American Journal of Pathology, vol. 183, no. 1, p. 173–181, 2013.

[79] H. Schwertz, S. Koster, W. H. A. Kahr et al., “Anucleate platelets generate progeny,” Blood, vol. 115, no. 18, p. 3801–3809, 2010.

[80] A. M. Butkiewicz, H. Kemona, V. Dymicka-Piekarska, J. Matowicka-Karna, P. Radziwon, and A. Lipska., “Platelet count, mean platelet volume and thrombocytopoietic indices in healthy women and men.,” Thrombosis Research, vol. 118, no. 2, p. 199–204, 2006.

[81] M. Yazici, A. Kaya, Y. Kaya, S. Albayrak, H. Cinemre, and H. Ozhan., “Lifestyle modification decreases the mean platelet volume in prehypertensive patients.,” Platelets, vol. 20, no. 1, pp. 58-63, 2009.

[82] J. D. Eicher, N. Chami, T. Kacprowski et al., “Platelet-related variants identified by exomechip meta-analysis in 157,293 individuals.,” The American Journal of Human Genetics, vol. 99, no. 1, pp. 40-55, 2016.

[83] T. J. Kunicki and D. J. Nugent., “The genetics of normal platelet reactivity.,” Blood, vol. 116, no. 15, p. 2627–2634, 2010.

[84] T. J. Kunicki, S. A. Williams, and D. J. Nugent., “Genetic variants that affect platelet function.,” Current Opinion in Hematology, vol. 19, no. 2, p. 371–379, 2012.

[85] K. Shameer, J. C. Denny, K. Ding et al, “A genome- and phenome-wide association study to identify genetic variants influencing platelet count and volume and their pleiotropic effects.,” Human Genetics, vol. 133, no. 1, p. 95–109, 2014.

[86] Segel GB, Halterman MW, Lichtman MA., “The paradox of the neutrophil’s role in tissue injury.,” J Leukoc Biol., vol. 89, no. 3, pp. 359-72, 2011.

[87] Kolaczkowska E, Kubes P., “Neutrophil recruitment and function in health and infl ammation.,” Nat Rev Immunol., vol. 13, no. 3, p. 159–75, 2013.

[88] Jin R, Yang G, Li G., “Inflammatory mechanisms in ischemic stroke: role of inflammatory cells.,” J Leukoc Biol., vol. 87, no. 5, pp. 779-89, 2010.

[89] Ruf W, Ruggeri ZM., “Neutrophils release brakes of coagulation.,” Nat Med., vol. 16, no. 8, p. 851–2., 2010.

[90] Mocsai A., “Diverse novel functions of neutrophils in immunity, inflammation, and beyond.,” J Exp Med., vol. 210, no. 7, p. 1283–99, 2013.

[91] Carbone F, Nencioni A, Mach F, Vuilleumier N, Montecucco F., “Pathophysiological role of neutrophils in acute myocardial infarction.,” Thromb Haemost., vol. 110, no. 3, pp. 501-14, 2013.

[92] Wang Q, Tang XN, Yenari MA, “The inflammatory response in stroke.,” J Neuroimmunol, vol. 184, no. 1-2, pp. 53-68, 2007.

[93] Nilupul Perera M, Ma HK, Arakawa S, Howells DW, Markus R, Rowe CC, Donnan GA, “Inflammation following stroke.,” J Clin Neurosci, vol. 13, no. 1, pp. 1-8, 2006.

[94] Kim JS., “Cytokines and adhesion molecules in stroke and related diseases,” J Neurol Sci, vol. 137, no. 2, pp. 69-78, 1996.

[95] Yilmaz G, Granger DN, “Cell adhesion molecules and ischemic stroke,” Neurol Res, vol. 30, no. 8, p. 783–793, 2008.

[96] Arvin B, Neville LF, Barone FC, Feuerstein GZ, “The role of inflammation and cytokines in brain injury,” Neurosci Biobehav Rev, vol. 20, no. 3, p. 445–452, 1996.

[97] Hartl R, Schurer L, Schmid-Schonbein GW, del Zoppo GJ, “Experimental antileukocyte interventions in cerebral ischemia,” J Cereb Blood Flow Metab, vol. 16, no. 6, p. 1108–1119, 1996.

[98] Chopp M, Li Y, Jiang N, Zhang RL, Prostak J, “Antibodies against adhesion molecules reduce apoptosis after transient middle cerebral artery occlusion in rat brain,” J Cereb Blood Flow Metab, vol. 16, no. 4, p. 578–584, 1996.

[99] Cep Juli, Henhen Heryaman, Arnengsih Nazir, Eng-Tat Ang,Irma Ruslina Defi, Uni Gamayani, and Nur Atik, “The Lymphocyte Depletion in Patients with Acute Ischemic Stroke Associated with Poor Neurologic Outcome,” Int J Gen Med. , vol. 14, pp. 1843-1851, 2021.

[100] Ren H, Liu X, Wang L, Gao Y, “Lymphocyte-to-monocyte ratio:a novel predictor of the prognosis of acute ischemic stroke,” J Stroke Cerebrovasc, vol. 26, no. 11, p. 2595–2602, 2017.

[101] Jennifer C Felger, Takato Abe, Ulrike W Kaunzner, Andres Gottfried-Blackmore, Judit Gal-Toth, Bruce S McEwen, Costantino Iadecola, Karen Bulloch, “Brain dendritic cells in ischemic stroke: time course, activation state, and origin,” Brain Behav Immun, vol. 24, no. 5, pp. 724-737, 2010.

[102] R Tanaka, M Komine-Kobayashi, H Mochizuki, M Yamada, T Furuya, M Migita, T Shimada, Y Mizuno, T Urabe, “Migration of enhanced green fluorescent protein expressing bone marrow-derived microglia/macrophage into the mouse brain following permanent focal ischemia,” Neuroscience, vol. 117, no. 3, p. 531–539, 2003.

[103] Shao, Y.; Wu, B.; Jia, W.; Zhang, Z.; Chen, Q.; Wang, D., “Prognostic value of pretreatment neutrophil-to-lymphocyte ratio in renal cell carcinoma: A systematic review and meta-analysis.,” BMC Urol. 2020, vol. 20, no. 90, 2020.

[104] Gao, X.; Coull, B.; Lin, X.; Vokonas, P.; Sparrow, D.; Hou, L.; DeMeo, D.L.; Litonjua, A.A.; Schwartz, J.; Baccarelli, A.A., “Association of Neutrophil to Lymphocyte Ratio with

Pulmonary Function in a 30-Year Longitudinal Study of US Veterans.," JAMA Netw. Open, vol. 3, no. 7, p. e2010350, 2020.

[105] Li, K.J.; Xia, X.F.; Su, M.; Zhang, H.; Chen, W.H.; Zou, C.L., "Predictive value of lymphocyte-to-monocyte ratio (LMR) and neutrophil-to-lymphocyte ratio (NLR) in patients with oesophageal cancer undergoing concurrent chemoradiotherapy," BMC Cancer, vol. 19, no. 1004, 2019.

[106] Rodrigues, S.F.; Granger, D.N., "Leukocyte-mediated tissue injury in ischemic stroke.," Curr. Med. Chem., vol. 21, p. 2130–2137, 2014.

[107] Song, S.Y.; Zhao, X.X.; Rajah, G.; Hua, C.; Kang, R.J.; Han, Y.P.; Ding, Y.C.; Meng, R., "Clinical Significance of Baseline Neutrophilto–to–Lymphocyte Ratio in Patients with Ischemic Stroke or Hemorrhagic Stroke: An Updated Meta-Analysis.," Front. Neurol., vol. 10, p. 1032, 2019.

[108] Goyal, N.; Tsivgoulis, G.; Chang, J.J.; Malhotra, K.; Pandhi, A.; Ishfaq, M.F.; Alsbrook, D.; Arthur, A.S.; Elijovich, L.;Alexandrov, A.V., "Admission Neutrophil-to-Lymphocyte Ratio as a Prognostic Biomarker of Outcomes in Large Vessel Occlusion strokes," stroke, vol. 49, pp. 1985-1987, 2018.

[109] Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC,Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D., "The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions explanation and elaboration.," J Clin Epidemiol, vol. 62, pp. e1-34, 2009.

[110] Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD,Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB, "Metaanalysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group.," JAMA, vol. 283, pp. 2008-2012, 2000.

[111] Stang A., “Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses.,” Eur J Epidemiol, vol. 25, pp. 603-605, 2010.

[112] Wan X, Wang W, Liu J, Tong T., “Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range.,” BMC Med Res Methodol, vol. 14, no. 135, 2014.

[113] Viechtbauer W., “Conducting meta-analyses in R with the metafor package.,” Journal of Statistical Software, vol. 36, no. 3, 2010.

[114] Huzsvai L, Balogh P., “Linear models using R. Debrecen, Hungary,” 2015.

[115] The European Stroke Organisation Executive Committee; ESO Writing Committee., “Guidelines for management of Ischemic stroke and transient Ischemic attack 2008.,” Cerebrovasc. Dis., vol. 25, pp. 457-507, 2008.

[116] Aviv, R.I.; Mandelcorn, J.; Chakraborty, S.; Gladstone, D.; Malham, S.; Tomlinson, G.; Fox, A.J.; Symons, S. Alberta Stroke Program, “Early CT Scoring of CT perfusion in early stroke visualization and assessment. Am.,” J. Neuroradiol., vol. 28, p. 1975–1980, 2007.

[117] Adams, H.P., Jr.; Bendixen, B.H.; Kappelle, L.J.; Biller, J.; Love, B.B.; Gordon, D.L.; Marsh, E.E., 3rd., “Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10,172 in Acute Stroke Treatment,” Stroke, vol. 24, p. 35–41, 1993.

[118] Hacke, W.; Kaste, M.; Bluhmki, E.; Brozman, M.; Davalos, A.; Guidetti, D.; Larrue, V.; Lees, K.R.; Medeghri, Z.; Machnig, T.; et al., “Thrombolysis with alteplase 3 to 4.5 h after acute ischemic stroke.,” N. Engl. J. Med., vol. 359, pp. 1317-1329, 2008.

[119] Simonsen, C.Z.; Schmitz, M.L.; Madsen, M.H.; Mikkelsen, I.K.; Chandra, R.V.; Leslie-Mazwi, T.; Andersen, G., “Early neurological deterioration after thrombolysis: Clinical and imaging predictors.,” Int. J. Stroke., vol. 11, p. 776–782, 2016.

[120] Wan X, Wang W, Liu J, Tong T., “Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range,” BMC Med Res Methodol, vol. 14, 2014.

[121] D’Erasmo E, Celi FS, Acca M, Mazzuoli G., “Relationship between platelet and white blood cell counts during the early phase of cerebral infarction,” Stroke, vol. 22, p. 283, 1991.

[122] Falke P, Lindgärde F, Stavenow L., “Differences in blood viscosity,glycosylated hemoglobin and platelet count between male patients with carotid territory transient ischemic attacks and minor strokes.,” Clinical Hemorheology, vol. 11, pp. 35-40, 1991.

[123] O’Malley T, Langhorne P, Elton RA, Stewart C., “Platelet size in stroke patients,” Stroke, vol. 26, pp. 995-999, 1995.

[124] Giroud M, Creisson E, Fayolle H, Andre N, Becker F, Martin D,Dumas R., “ Risk factors for primary cerebral hemorrhage:a population-based study–the Stroke Registry of Dijon.,” Neuroepidemiology, vol. 14, pp. 20-26, 1995.

[125] O’Malley T, Lahghorne P, Stehart C, “Do large platelets cause stroke?” Age and Aging, vol. 23, pp. P3-cIp3, 1994.

[126] Butterworth RJ, Bath PM, “The relationship between mean platelet volume, stroke subtype and clinical outcome.,” Platelets, vol. 9, pp. 359-364, 1998.

[127] Smith NM, Pathansali R, Bath PM., “Altered megakaryocyte-platelet haemostatic axis in patients with acute stroke.,” Platelets, vol. 13, pp. 113-120, 2002.

[128] Ziai WC, Torbey MT, Kickler TS, Oh S, Bhardwaj A, Wityk RJ., “Platelet count and function in spontaneous intracerebral hemorrhage.,” J Stroke Cerebrovasc Dis 2003, vol. 12, pp. 201-206, 2003.

[129] Cha JK, Jo WS, Shin HC, Bae HR, Ho JM, Kim JW., “Increased platelet CD63 and P-selectin expression persist in atherosclerotic ischemic stroke.,” Platelets, vol. 15, pp. 3-7, 2004.

[130] Wolff V, Aleil B, Giroud M, Lorenzini JL, Meyer N, Wiesel ML, “Cazenave JP, Lanza F. Soluble platelet glycoprotein V is a marker of thrombosis in patients with ischemic stroke,” Stroke, vol. 36, p. e17–19., 2005.

[131] Sadreddini SA, Abolfathi AA, Khandagi R, Talebi M, Lakian A., “C-reactive protein, fibrinogen, lipoprotein (a), and lipid profile levels and platelet counts in ischemic stroke patients.,” Neurosciences (Riyadh), vol. 12, pp. 202-206, 2007.

[132] Ilhan D, Ozbabalik D, Gulcan E, Ozdemir O, Gulbacs Z., “Evaluation of platelet activation, coagulation, and fibrinolytic activation in patients with symptomatic lacunar stroke.,” Neurologist, vol. 16, pp. 188-191, 2010.

[133] Mayda-Domac F, Misirli H, Yilmaz M., “Prognostic role of mean platelet volume and platelet count in ischemic and hemorrhagic stroke.,” J Stroke Cerebrovasc Dis, vol. 19, pp. 66-72, 2010.

[134] Al-Tameemi WF, Ameen AMM., “Significance of platelet indices in patients with acute ischemic stroke.,” Iraqi Journal of Medical Sciences, vol. 10, pp. 383-389, 2011.

[135] Jaremo P, Eriksson M, Lindahl TL, Nilsson S, Milovanovic M., “Platelets and acute cerebral infarction.,” Platelets, vol. 24, pp. 407-411, 2013.

[136] Cho SY, Jeon YL, Choi SK, Suh JT, Lee HJ, Park TS., “Mean platelet volume in Korean patients with acute ischemic stroke: a gender difference,” Platelet, vol. 24, pp. 75-76, 2013.

[137] Dogan NO, Keles A, Aksel G, Guler S, Demircan A, Bildik F,Kilicaslan I, Karakurt K, Ilhan M. , “Mean platelet volume as a risk stratification tool in the emergency department for evaluating patients with Ischemic stroke and TIA,” J Pak Med Assoc, vol. 65, pp. 581-584, 2013.

[138] Celikbilek A, Ismailogullari S, Zararsiz G., “Neutrophil to lymphocyte ratio predicts poor prognosis in ischemic cerebrovascular disease.,” J Clin Lab Anal, vol. 28, pp. 27-31, 2014.

[139] Li B, Liu X, Cao ZG, Li Y, Liu TM, Wang RT, “Elevated mean platelet volume is associated with silent cerebral infarction.,” Intern.Med. J, vol. 44, pp. 653-657, 2014.

[140] Ozkan B, Arik OZ, Gozukara MY, Sahin DY, Topal S, Uysal OK,Elbasan Z, EpcelidenT, CayliM,Gur M. , “Mean platelet volume is related with ischemic stroke in patients with sinus rhythm.,” Blood Coagulation & Fibrinolysis, vol. 27, no. 5, pp. 490-493, 2016.

[141] Wang D, Zhang FH, Zhao YT, Xiao XG, Liu S, Shi HB, Lin AL,Wang YJ, Han Q, Sun QM., “Association of polymorphism in ICAM-1 (K469E) and cytology parameters in patients’ initial blood test with acute ischemic stroke.,” Genet Mol Res, vol. 14, pp. 15520-15529, 2015.

[142] Lee JM, Siddique J, Kim HC, Green D, Van Horn L, Allison M,Wassertheil-Smoller S, Greenland P., “Hemostatic markers and long-term risk of intracerebral hemorrhage in postmenopausal woman,” J Stroke Cerebrovasc Dis, vol. 25, pp. 1639-1643, 2016.

[143] Oz II, Yucel M, Bilici M, Serifoglu I, Sayin R, Ilikhan SU,Acikgoz M., “Is mean platelet volume a reliable marker to predict ischemic stroke in the follow-up of patients with carotid stenosis?,” J Stroke Cerebrovasc Dis, vol. 25, pp. 404-409, 2016.

[144] Elsayed AM, Mohamed AG, “Mean platelet volume and mean platelet volume/platelet count ratio as a risk stratification tool in the assessment of severity of acute ischemic stroke.,” Alexandria Journal of Medicine, vol. 53, pp. 67-70, 2017.

[145] Wan JL, Ma ZW., “The value of mean platelet volume for prognosis of patients with acute cerebral infarction.,” Clin Lab, vol. 63, pp. 1801-1807, 2017.

[146] Patel V, Parmar M, Shah K, Joshi R. A study on mean platelet, “A study on mean platelet volume in ischemic cerebrovascular stroke. International Journal of,” International Journal of Advances in Medicine, vol. 5, pp. 316-320, 2018.

[147] Farah R, Samra N., “Mean platelets volume and neutrophil to lymphocyte ratio as predictors of stroke,” J Clin Lab Anal, vol. 32, 2018.

[148] Sarkar RN, Das CK, Bhattacharjee U, Banerjee M., “Platelet indices as a marker of severity in non-diabetic nonhypertensive acute ischemic stroke patients.,” J Assoc Physicians India, vol. 66, pp. 40-42, 2018.

[149] D’Erasmo E, Aliberti G, Celi FS, Romagnoli E, Vecci E,Mazzuoli GF., “Platelet count, mean platelet volume and their relation to prognosis in cerebral infarction,” J Intern Med, vol. 227, pp. 11-14, 1990.

[150] Ayas ZO, Can U., “Alteration of mean platelet volume in the pathogenesis of acute ischemic stroke: cause or consequence?” Ideggyogy Sz, vol. 71, pp. 49-56, 2018.

[151] Thompson CB, Eaton KA, Princiotta SM, Rushin CA, Valeri CR., “Size dependent platelet subpopulations: relationship of platelet volume to ultrastructure, enzymatic activity, and function.,” Br J Haematol, vol. 50, pp. 509-519, 1982.

[152] Rajajee V, Brown DM, Tuhrim S., “Coagulation abnormalities following primary intracerebral hemorrhage,” J Stroke Cerebrovasc Dis, vol. 13, pp. 47-51, 2004.

[153] Weymann A, Ali-Hasan-Al-Saegh S, Sabashnikov A, Popov AF,Mirhosseini SJ, Nombela-Franco L, Testa L, Lotfaliani M,Zeriouh M, Liu T, et al, “ Surgery, Cardiology-Group Imcsc-Group IM. Platelets cellular and functional characteristics in patients with atrial fibrillation: a comprehensive meta-analysis and systematic review,” Med Sci Monit Basic Res, vol. 23, pp. 58-86, 2017.

[154] Lin WY, Lu X, Fan FJ, Hu Y., “Predictive effect of mean platelet volume in patients with portal vein thrombosis: a meta-analysis of case-control studies.,” Curr Med Sci, vol. 38, pp. 575-581, 2018.

[155] Gasparyan AY, Ayvazyan L, Mikhailidis DP, Kitas GD, “Mean platelet volume: a link between thrombosis and inflammation?” Curr Pharm Des, vol. 17, pp. 47-58, 2011.

[156] Li Z, Wang J, Han X, Yuan J, Guo H, Zhang X, Zheng D, Tang Y,Yang H, He M., “ Association ofmean platelet volumewith incident type 2 diabetes mellitus risk: the Dongfeng-Tongji cohort study.,” Diabetol Metab Syndr, vol. 10, no. 29, 2018.

[157] Varol E, Aksoy F, Bas HA, Ari H, Ozaydin M., “Mean platelet volume is elevated in patients with low high-density lipoprotein cholesterol.,” Angiology, vol. 65, pp. 733-736, 2014.

[158] Gang L, Yanyan Z, Zhongwei Z, Juan D., “Association between mean platelet volume and hypertension incidence.,” Hypertens Res, vol. 40, pp. 779-784, 2017.

[159] Varol E, Icli A, Kocyigit S, Erdogan D, Ozaydin M, Dogan, “A. Effect of smoking cessation on mean platelet volume.,” Clin Appl Thromb Hemost, vol. 19, pp. 315-319, 2013.

[160] Zaccardi F, Rocca B, Pitocco D, Tanese L, RizziA,Ghirlanda G. , “Platelet mean volume, distribution width, and count in type 2 diabetes, impaired fasting glucose, and metabolic syndrome: a meta-analysis.,” Diabetes Metab Res Rev, vol. 31, pp. 402-410, 2015.

[161] Sansanayudh N, Numthavaj P, Muntham D, Yamwong S,McEvoy M, Attia J, Sritara P, Thakkinstian A. , “Prognostic effect of mean platelet volume in patients with coronary artery disease.A systematic review and meta-analysis.,” Thromb Haemost, vol. 114, pp. 1299-1309, 2015.

[162] Chu SG, Becker RC, Berger PB, Bhatt DL, Eikelboom JW, Konkle B,Mohler ER, ReillyMP, Berger JS., “Mean platelet volume as a predictor of cardiovascular risk: a systematic review and meta-analysis.,” J Thromb Haemost, vol. 8, pp. 148-156, 2010.

[163] Kamath S, Blann AD, Lip GY., “Platelet activation: assessment and quantification.,” Eur Heart J, vol. 22, pp. 1561-1571, 2001.

[164] Thon JN, Italiano JE Jr., “Does size matter in platelet production?” Blood, vol. 120, pp. 1552-1561, 2012.

[165] McCabe DJ, Harrison P, Mackie IJ, Sidhu PS, Purdy G, Lawrie AS,Watt H, Brown MM, Machin SJ, “Platelet degranulation and monocyte-platelet complex formation are increased in

the acute and convalescent phases after Ischemic stroke or transient Ischemic attack," Br J Haematol, vol. 125, pp. 777-787, 2004.

[166] McCabe DJ, Harrison P, Sidhu PS, Brown MM, Machin SJ., "Circulating reticulated platelets in the early and late phases after Ischemic stroke and transient Ischemic attack.," Br J Haematol, vol. 126, pp. 861-869, 2004.

[167] Mulley GPHS, Taylor PM, Mitchell JR., "ADP-induced platelet release reaction in acute stroke.," Thrombosis and Haemostasis, vol. 50, no. 3, 1983.

[168] Reardon DM, Hutchinson D, Preston FE, Trowbridge EA., "The routine measurement of platelet volume: a comparison of aperture-impedance and flow cytometric systems," Clin Lab Haematol, no. 3, pp. 251-257, 1985.

[169] Diaz-Ricart M, Brunso L, Pino M, Navalon F, Jou JM, Heras M,White JG, Escolar G. , "Preanalytical treatment of EDTA-anticoagulated blood to ensure stabilization of the mean platelet volume and component measured with the ADVIA counters.," Thromb Res, vol. 126, pp. e30-35, 2010.

[170] Gachet C, Hanau D, Spehner D, Brisson C, Garaud JC, Schmitt DA,Ohlmann P, Cazenave JP., "Alpha IIb beta 3 integrin dissociation induced by EDTA results in morphological changes of the platelet surface-connected canalicular system with differential location o the two separate subunits.," J Cell Biol, vol. 120, pp. 1021-1030, 1993.

[171] Kecskemetine G, Csiki Z, Mile M, Zsori KS, Shemirani AH., "The clinical significance of pneumatic tube transport system on platelet indices: EDTA or citrate anticoagulant?" Int J Lab Hematol, vol. 39, pp. e102-e105, 2017.

[172] McShine RL, Sibinga S, Brozovic B., "Differences between the effects of EDTA and citrate anticoagulants on platelet count and mean platelet volume.," Clin Lab Haematol, vol. 12, pp. 277-285, 1990.

[173] Trowbridge EA, Reardon DM, Hutchinson D, Pickering C., “The routine measurement of platelet volume: a comparison of light-scattering and aperture-impedance technologies. Clin Phys,” Clin Physics and Physiol Meas, vol. 6, pp. 221-238, 1985.

[174] Mannuss S, Schuff-Werner P, Dreissiger K, Kohlschein P., “Magnesium Sulfate as an Alternative In Vitro Anticoagulant for the Measurement of Platelet Parameters?” AmJ Clin Pathol, vol. 145, pp. 806-814, 2016.

[175] Jin, R.; Yang, G.; Li, G., “Inflammatory mechanisms in ischemic stroke: Role of inflammatory cells.,” J. Leukoc. Biol., vol. 87, pp. 779-789, 2010.

[176] Chiba, T.; Umegaki, K., “Pivotal roles of monocytes/macrophages in stroke.,” Mediat. Inflamm, vol. 2013, 2013.

[177] Kolaczkowska, E.; Kubes, P., “Neutrophil recruitment and function in health and inflammation.,” Nat. Rev. Immunol, vol. 13, pp. 159-175, 2013.

[178] Nilupul Perera, M.; Ma, H.K.; Arakawa, S.; Howells, D.W.; Markus, R.; Rowe, C.C.; Donnan, G.A., “Inflammation following stroke.,” J. Clin. Neurosci, vol. 13, pp. 1-8, 2006.

[179] Simoni, M.G.D., “Two-way communication pathways between the brain and the immune system.,” Neurosci. Res. Commun, vol. 21, pp. 163-172, 1997.

[180] Jickling, G.C.; Liu, D.; Ander, B.P.; Stamova, B.; Zhan, X.; Sharp, F.R., “Targeting neutrophils in ischemic stroke: Translational insights from experimental studies,” J. Cereb. Blood Flow Metab, vol. 35, pp. 888-901, 2015.

[181] Ruhnau, J.; Schulze, J.; Dressel, A.; Vogelgesang, “A. Thrombosis, Neuroinflammation, and Poststroke Infection: The Multifaceted Role of Neutrophils in Stroke,” J. Immunol. Res., vol. 2017, 2017.

[182] Shi, J.; Peng, H.; You, S.; Liu, Y.; Xu, J.; Xu, Y.; Liu, H.; Shi, R.; Cao, Y.; Liu, C.F., “Increase in neutrophils after recombinant tissue plasminogen activator thrombolysis predicts

poor functional outcome of Ischemic stroke: A longitudinal study.," Eur. J. Neurol., vol. 25, no. 4, pp. 687-e45, 2018.

[183] Brooks, S.D.; Spears, C.; Cummings, C.; VanGilder, R.L.; Stinehart, K.R.; Gutmann, L.; Domico, J.; Culp, S.; Carpenter, J.;Rai, A.; et al., "Admission neutrophil-lymphocyte ratio predicts 90 day outcome after endovascular stroke therapy.," J. Neurointerv., vol. 6, pp. 578-583, 2014.

[184] Lux, D.; Alakbarzade, V.; Bridge, L.; Clark, C.N.; Clarke, B.; Zhang, L.; Khan, U.; Pereira, A.C., "The association of neutrophil-lymphocyte ratio and lymphocyte-monocyte ratio with 3-month clinical outcome after mechanical thrombectomy following stroke," J. Neuroinflamm. , vol. 17, 2020.

[185] Pektezel, M.Y.; Yilmaz, E.; Arsava, E.M.; Topcuoglu, M.A, "Neutrophil-to-Lymphocyte Ratio and Response to Intravenous Thrombolysis in Patients with Acute Ischemic Stroke," J. Stroke Cerebrovasc. Dis, vol. 28, pp. 1853-1859, 2019.

[186] Wang, C.; Zhang, Q.; Ji, M.; Mang, J.; Xu, Z., "Prognostic value of the neutrophil-to-lymphocyte ratio in acute ischemic stroke patients treated with intravenous thrombolysis: A systematic review and meta-analysis," BMC Neuro, vol. 21, 2021.

[187] Switonska, M.; Slomka, A.; Korbal, P.; Piekus-Slomka, N.; Sinkiewicz,W.; Sokal, P.; Zekanowska, E., "Association of Neutrophilto-to-Lymphocyte Ratio and Lymphocyte-to-Monocyte Ratio with Treatment Modalities of Acute Ischemic Stroke: A Pilot Study.," Medicina , vol. 55, no. 7, p. 342, 2019.

[188] Dong, X.; Nao, J.; Gao, Y., "Peripheral Monocyte Count Predicts Outcomes in Patients with Acute Ischemic Stroke Treated with rtPA Thrombolysis.," Neurotox. Res. , vol. 37, p. 469–477, 2020.

[189] ElAli, A.; Jean LeBlanc, N., "The Role of Monocytes in Ischemic Stroke Pathobiology: New Avenues to Explore. Front. Aging," Neurosci, vol. 8, no. 29, 2016.

[190] Wattananit, S.; Tornero, D.; Graubardt, N.; Memanishvili, T.; Monni, E.; Tatarishvili, J.; Miskinyte, G.; Ge, R.; Ahlenius, H.;Lindvall, O.; et al., “Monocyte-Derived Macrophages Contribute to Spontaneous Long-Term Functional Recovery after Stroke in Mice.,” J. Neurosci, vol. 36, pp. 4182-4195, 2016.

[191] Ren, H.; Han, L.; Liu, H.;Wang, L.; Liu, X.; Gao, Y., “Decreased Lymphocyte-to-Monocyte Ratio Predicts Poor Prognosis of Acute Ischemic Stroke Treated with Thrombolysis,” Med. Sci. Monit. Int. Med. J. Exp. Clin. Res., vol. 23, pp. 5826-5833, 2017.

[192] Gill, D.; Sivakumaran, P.; Aravind, A.; Tank, A.; Dosh, R.; Veltkamp, R., “Temporal Trends in the Levels of Peripherally Circulating Leukocyte Subtypes in the Hours after Ischemic Stroke.,” J. Stroke Cerebrovasc. Dis, vol. 27, pp. 198-202, 2018.

[193] Kim, J.; Song, T.J.; Park, J.H.; Lee, H.S.; Nam, C.M.; Nam, H.S.; Kim, Y.D.; Heo, J.H., “Different prognostic value of white blood cell subtypes in patients with acute cerebral infarction.,” Atherosclerosis, vol. 222, pp. 464-467, 2012.

[194] Liesz, A.; Hu, X.; Kleinschnitz, C.; Offner, H., “Functional role of regulatory lymphocytes in stroke: Facts and controversies,” stroke, vol. 46, pp. 1422-1430, 2015.

[195] Abo, T.; Kawamura, T., “Immunomodulation by the Autonomic Nervous System: Therapeutic Approach for Cancer, Collagen Diseases, and Inflammatory Bowel Diseases.,” Ther. Apher, vol. 6, pp. 348-357, 2002.

[196] Tracey, K.J., “The inflammatory reflex,” Nature, vol. 420, pp. 853-859, 2002.

[197] Fang, Y.N.; Tong, M.S.; Sung, P.H.; Chen, Y.L.; Chen, C.H.; Tsai, N.W.; Huang, C.J.; Chang, Y.T.; Chen, S.F.; Chang, W.N.; et al., “Higher neutrophil counts and neutrophil-to-lymphocyte ratio predict prognostic outcomes in patients after non-atrial fibrillation-caused ischemic stroke.,” Biomed. J., vol. 40, pp. 154-162, 2017.

[198] Xue, J.; Huang, W.; Chen, X.; Li, Q.; Cai, Z.; Yu, T.; Shao, B., "Neutrophil-to-Lymphocyte Ratio Is a Prognostic Marker in Acute Ischemic Stroke," J. Stroke Cerebrovasc. Dis., vol. 26, p. 650–657, 2017.

[199] Semerano, A.; Laredo, C.; Zhao, Y.; Rudilosso, S.; Renu, A.; Llull, L.; Amaro, S.; Obach, V.; Planas, A.M.; Urra, X.; et al., "Leukocytes,Collateral Circulation, and Reperfusion in Ischemic Stroke Patients Treated with Mechanical Thrombectomy," stroke, vol. 50, pp. 3456-3464, 2019.

[200] Deirdre A; Lane; Gregory Y.H. Lip; "Use of the CHA2DS2-VASc and HAS-BLED Scores to Aid Decision Making for Thromboprophylaxis in Nonvalvular Atrial Fibrillation" Circulation, vol. 126, pp. 860-865, 2012.

[201] Glen C. Jickling; Frank R. Sharp "Roles of Neutrophils in Stroke", Journal of Cerebral Blood Flow Metabolism", vol. 35, p.888-901, 2015.

[202] Diego L, Andrea G.V; "Brain regions that support accurate speech production after damage to Broca's area", Brain communications, vol.3,2021.

[203] Tohgi H; Suzuki H; Tamura K, Kimura B; "Platelet volume, aggregation, and adenosine triphosphate release in cerebral thrombosis" Stroke, vol.22, pp.17–21, 1991.

[204] Gokdemir MT; Karakilcik AZ; Gokdemir GS; "Prognostic importance of paraoxonase, arylesterase and mean platelet volume efficiency in acute ischaemic stroke", J Pak Med Assoc, vol.67,1679–1683, 2017.

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   Platelets. 31 (6), 731-739, 2020.
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