



# Neutrophil-to-lymphocyte Ratio and Platelet-to-lymphocyte Ratio as an Inflammatory Biomarker in Predicting the Severity of Secondary Brain Injury: A Review Article

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## Abstract

Traumatic brain injury (TBI) is one of the leading causes of death and disability, which affects millions of people globally with a significant economic burden. The inflammatory reactions and immune system activity play a significant role in the severity development of secondary brain injury (SBI) after a TBI event. Neutrophils, platelets, and lymphocytes are involved in these inflammatory reactions and have potential in reflecting the severity level of SBI that occurred post-TBI. Some recent studies have shown that the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) can be used as a potential biomarker for determining the severity of an inflammatory reaction, including SBIs in post-TBI. However, the results of NLR and PLR in TBI patients in daily medical practice are still not fully utilized. This review summarizes the neutrophil's, platelet's, and lymphocyte's role in SBI, also the NLR and PLR potential as a marker of the severity of the SBI process in TBI cases.

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## Introduction

Traumatic brain injury (TBI) is one of the leading causes of death and disability, which affects millions of people globally with a significant economic burden [1]. It can lead to impaired cognitive and physical functions that can be suffered by the patients for the rest of their life. Those problems may cause the patients to spend costs and efforts because they require prolonged treatment and rehabilitation to recover their disability [2]. Therefore, comprehensive initial management is needed, which includes the biomarker examination that can predict the severity of secondary brain injury (SBI) in TBI patients. Thus, the effectiveness of the TBI's treatment can be increased, and the progression of the SBI in TBI cases can be prevented.

TBI is an injury caused by the external mechanical force to the cranium and its intracranial components, thus alters the brain structures and functions [3]. The pathologic processes that occur in

the TBI consist of the primary and SBI [4]. Primary brain injury is caused by the exposure of mechanical force to the brain tissue, which leads to axonal damages, vascular damages, and glial cells damages. A SBI is caused by the occurrence of the inflammatory cascades that are initiated by the release of various inflammatory factors and neurotransmitters from the damaged neuronal and glial cells in the brain [5].

SBI is sensitive toward the treatment, and its processes can be prevented. SBI is an essential therapeutic window and can determine whether the development and recovery of the TBI are good or bad [5]. The increase in the systemic inflammatory response can be reflected from increased inflammatory cells, such as neutrophils, or the increase in the level of the inflammatory biomarkers, such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) [6], [7]. CRP and ESR are already commonly used to monitor the progression of inflammatory diseases, but these laboratory examinations have not been routinely done in traumatic patients. Moreover, CRP and ESR

examinations are also not always available in every hospital.

On the other hand, the neutrophils, platelets, and lymphocytes count can be obtained through a complete blood count (CBC), which is more routinely done compared to the CRP and ESR laboratory examinations in the traumatic patients. The CBC examination is used primarily to monitor the bleeding that occurs due to trauma through the hemoglobin's and hematocrit's level. The CBC test is also available in every hospital, even in some rural areas. A CBC test is undoubtedly a cheaper and more available laboratory examination in daily medical practice [8].

Some recent studies have shown that the neutrophil-to-lymphocyte ratio (NLR) is very easy to be measured and can act as a predictor of clinical outcomes from cancer, cardiovascular, and stroke diseases [9], [10], [11]. Besides NLR, the platelet-to-lymphocyte ratio (PLR) can also act as a potential marker for determining the severity of an inflammatory reaction [7]. Moreover, a study found that NLR and PLR are positively correlated with high sensitivity CRP (hs-CRP) and ESR in patients with autoimmune inflammatory disease, such as Takayasu's Arteritis [7]. However, the predictive value of NLR and PLR in TBI cases is still unclear and has not been extensively explored.

Theoretically, NLR and PLR have the potential to be used as a marker of the severity of the SBI process that occurs in TBI. However, the results of NLR and PLR in TBI patients in daily medical practice are still not fully utilized. This review will summarize the neutrophil's, platelet's, and lymphocyte's role in SBI, also the NLR and PLR potential as a marker of the severity of the SBI process in TBI cases.

## Methods

This article used a literature review method. Journals from various accredited and online-based sources such as PubMed and Google Scholar database are collected using the following keywords: NLR, PLR, TBI, SBI, inflammation, neutrophil, platelet, and lymphocyte. A total of 110 articles relevant to the topic were included and reviewed for the analysis and synthesis process.

## Results and Discussion

### **SBI**

SBI begins immediately after the primary brain injury and can trigger a series of events that cause

cerebral edema, cerebral ischemia, and even death or persistent vegetative condition [12], [13]. The immune system activity and inflammation response have been proved as the crucial factors in initiating and developing the SBI processes to a more severe state post-TBI [14], [15]. Cells such as neutrophils, astrocytes, and microglia are involved in the acute inflammation reactions post-TBI [16].

Under physiologic conditions, the brain is an organ that has special immunity due to the presence of blood-brain barrier (BBB), a limited number of antigen-presenting cells (APC), and a few apparent lymphatic vessels [17]. However, TBI can cause direct damage to the BBB, which allows the entry of massive amounts of peripheral APCs, as well as activation of microglia in the damaged brain [4], [18]. In addition, the latest research shows another new passage through the lymphatic blood vessels in the central nervous system's (CNS) meninges for the peripheral immune cells to enter the brain's tissue back and forth [19]. All of these things can interfere with the balance of the CNS's immune system environment, which can cause communication between the peripheral immune system and the CNS in TBI [20].

The damaged blood vessels will cause the blood to come out of the blood vessels, thereby disrupting the blood supplies and BBB integrity in the brain's tissue. The damaged neurons and glial cells also can induce an inflammatory cascade response by releasing various inflammatory factors and neurotransmitters post-TBI. Processes that can occur in the SBI include aggravate of the BBB damages, change in the blood flow (ischemia, bleeding), neuroinflammation, dysfunction of the metabolism in the brain's tissue (edema and hypoxia), and cell damage (oxidative stress, excitotoxicity, production of free radicals, and apoptosis/necrosis of the neurons) [5].

### **Neutrophil's roles in SBI**

Neutrophils are the primary component in the innate immune system that plays an essential role in the acute inflammation against pathogens and can cause tissue damages indiscriminately [5]. Due to the role of the BBB, there are only a few amounts of neutrophils that can be found in the brain's parenchyma [21]. However, pathological conditions such as trauma, bleeding, ischemia, and infection can cause an increase in the number of neutrophils that enter the brain's tissue [17].

External factors, such as trauma and stress, as well as internal factors, such as granulocyte-macrophage-colony stimulating factor (GM-CSF) and granulocyte-CSF (G-CSF), can modulate the neutrophil's activity [22], [23], [24]. These factors will make the neutrophils undergo the differentiation and maturation processes, which include the changes in the level of expression of the neutrophil's membrane proteins that are very crucial for neutrophils to sense the infection or danger signals; thus neutrophils

are able to move toward the target tissue and phagocytose the tissue debris [5]. These factors also increase the expression of various granule proteins in the neutrophils which are useful to eliminate the pathogens such as matrix metalloproteinases (MMPs), neutrophils elastase (NE), myeloperoxidase, and neutrophils gelatinase-associated lipocalin [25], [26]. The accumulation of neutrophils to eliminate pathogens through phagocytosis and degranulation processes is the first line of the immune system (innate immune system), but it can aggravate the tissue damages and SBI if too excessive [5].

The damaged brain's parenchyma post-TBI can release inflammatory cytokines such as tumor necrosis factor (TNF)- $\alpha$ , interleukin (IL)-1 $\beta$ , CXCL1, CXCL2, and CXCL5, which further activate the neutrophils and endothelial cells and facilitate the migration of the neutrophils into the CNS parenchyma [27], [28]. TBI also induces vascular damages in the brain, including the BBB. The activated neutrophils will accumulate in the damaged cortical and the disrupted BBB area within 12-h post-TBI, then migrate to the surrounding brain parenchyma within 24-h post-TBI [18]. The activated neutrophils can damage the tight junction and permeability of BBB by degrading the zonula occludens-1, vinculin, occludin, and  $\beta$ -catenin, which are very important for maintaining the integrity of BBB [5]. The NE and MMPs released by neutrophils can interfere the cadherin-cadherin bond, degrade the neurovascular structures and dysregulate the BBB, thus induce the hyper-permeability of the BBB [29], [30], [31], [32]. The activated neutrophils also release free radicals such as reactive oxygen species (ROS) and nitrous oxide, which induce the direct oxidative damages and disrupt the arrangement of claudin-5 and occludin in the endothelium, thus impair the integrity of BBB [33], [34]. The BBB damages due to neutrophils activity will facilitate the immune cell's recruitment into the brain parenchyma to fight against pathogens. However, it can also aggravate brain damages and SBI at the same time.

Neutrophils are also involved in the process of cerebral edema post-TBI. Cerebral edema is a state caused by the excessive fluid accumulation in the intracellular or extracellular spaces of the brain's tissue, which causes expansion or swelling of the brain's tissue in a limited skull cavity. It can increase the intracranial pressure, interfere with the brain's perfusion and oxygenation, and contribute to a more severe ischemic injury post-TBI [35]. Neutrophils are tightly related to cerebral edema in the SBI process post-TBI. The BBB damages, which are caused by neutrophils activity, enable the protein and intravascular fluid to enter and accumulate in the extracellular space of the brain's parenchyma, thus lead to cerebral edema [36]. In addition, granules that released by neutrophils such as elastase, lipoxin, and azurocidin can increase the vascular permeability, thus can also aggravate the cerebral edema [37], [38].

The activated neutrophils can also contribute to the imbalance between cerebral oxygen delivery and cerebral oxygen consumption in SBI post-TBI because they will consume more oxygen to produce and release the NADPH oxygenase-related molecules, hydrogen peroxide superoxide, and antibacterial proteins such as defensins and cathelicidin for maintaining its phagocytic function [4], [18], [33], [39]. Changes in the volume and rate of the cerebral blood flow and the arterial oxygen content post-TBI can interfere with the oxygen delivery, causing the injured area of the brain to experience a more hypoxic condition [5]. A previous study showed that the expression of NF $\kappa$ B and hypoxia-inducible factor-1 $\alpha$  could be induced by the low oxygen levels, which cause prolonged neutrophils survival and their activation [40]. Meanwhile, neutrophils themselves can also cause overproduction of ROS by the autocrine IL-17 pathway, which can aggravate the SBI due to ROS [41]. In addition, the clinical outcome of TBI patients is also correlated with the duration and severity of cerebral hypoxia that occurs in the SBI process [42]. Thus, the more neutrophils that activated in SBI post-TBI, the more cerebral hypoxia will occur, and the worse clinical outcome post-TBI will be.

Another crucial role of neutrophils in SBI is involved in the neuroinflammation process. Neuroinflammation is an inflammatory response in the CNS due to the reaction of brain cells and peripheral immune cells toward a stimulus or injury. Even though this response occurs to protect the CNS from damages and infections, neuroinflammation is also an essential mechanism to initiate the SBI process post-TBI [5]. Neuroinflammation due to TBI is characterized by the activated glial cells, leukocyte recruitment, and increased inflammatory cytokines regulation in the brain [43].

TBI can activate the microglia, which then induce the activation of endothelial cells and the peripheral leukocytes recruitment into the brain's tissue [44]. The activated microglia post-TBI will rearrange the expression pattern of their receptors and also release essential inflammatory mediators that are powerful for recruiting and activating neutrophils such as IL-1 $\beta$ , IL-6, CXCL1-5, CXCL8-10, and TNF- $\alpha$  [45]. Moreover, neutrophils themselves can also release molecules such as MMP9, lipocalin 2, and ROS, to mutually activate the microglia in an amplification cascade manner [46], [47], [48].

Astrocyte is also a glial cell that is the main constituent of the CNS. Astrocytes are essential for maintaining the CNS homeostasis and contributing to the integrity of BBB [5]. In TBI, neutrophils and astrocytes are closely linked and respond to each other to the cytokines that are released. Astrocytes are an essential source of cytokines such as IL-6, MMP2, MMP9, GM-CSF, CXCL1, CXCL2, CCL2, and chemokines containing glutamate-leucine-arginine motive [49]. Cytokines such as CXCL1, CXCL2, and



GM-CSF can increase the BBB disruption, increase the leukocyte recruitment, and initiate the inflammatory process [50], [51], [52]. IL-1 $\beta$  and TNF- $\alpha$  can inhibit the uptake of glutamate by astrocytes, thus aggravate the neuroinflammation [53]. Based on these data, neutrophils and astrocytes have an essential role in the neuroinflammation process as the primary source of cytokines and also exacerbate the inflammatory cascade reciprocally [5].

The activated neutrophils are able to release various chemokines and molecules that can affect the process of SBI (Table 1) [5]. After the danger signal disappeared, neutrophils are still challenging to be immediately stopped because they can also strengthen their activation through the autocrine mechanisms [56], [69], [70]. This process makes the neutrophils have the potential to indiscriminately damaged the brain's tissue and aggravate the SBI in TBI. Thus, to minimize the tissue damages after the digestion process of the pathogens by the neutrophils, most of the neutrophils are phagocytosed or inhibited by lymphocytes [5].

**Table 1: Various chemokines and molecules released by the activated neutrophils that can affect the process of SBI**

Name	Effect	Reference
IL-1 $\alpha$	Associated with BBB damage and neuronal death	[54]
IL-1 $\beta$	Induces neuronal death directly	[54]
IL-9	Exacerbates the excitotoxic brain damage	[55]
IL-18	Induces brain damage and induces neutrophils to secrete inflammatory cytokines	[56]
IL-23	Causes brain damage and neurological deficits	[57]
CXCL1	Recruits neutrophils to the injured brain	[58]
CXCL2	Facilitates the chemotaxis of polymorphonuclear leukocytes (PMN), peak in 4-h post-TBI	[59]
CXCL3	Facilitates the migration of neutrophils through the epithelial barrier	[60]
CXCL5	Increases microglia activation and BBB damage disrupt myelination	[61]
CXCL8	Helps neutrophils to infiltrate the brain parenchyma	[62]
M-CSF	Increases microglia activation	[63]
TNF- $\alpha$	Induces astrocytes to secrete IL-6 and IL-8, mediates the PMN neurotoxicity directly	[64]
ROS	Increases BBB dysfunction, causes neuronal cell death and microglia activation	[33]
MMP9	Damages BBB integrity, increases neutrophils infiltration and PMN neurotoxicity	[65]
MPO	Reflects the neutrophil infiltration in the brain tissue	[66]
Cathepsins	Causes cell death through programmed cell necrosis and the mitochondrial apoptotic pathway	[67]
NE	Induces acute neuronal death and cellular stress	[68]

TBI: Traumatic brain injury, SBI: Secondary brain injury, BBB: Blood-brain barrier, CSF: Colony-stimulating factor, MMP: Matrix metalloproteinases, NE: Neutrophils elastase, MPO: Myeloperoxidase, TNF: Tumor necrosis factor, IL: Interleukin, ROS: Reactive oxygen species.

### **Platelet's roles in SBI**

As mentioned previously, the immune system activity and the inflammatory response have been proven to play an important role in the initiation and development of the SBI process post-TBI to a more severe level [14], [15]. Not only neutrophils, astrocytes, and microglia but also platelets, which play an essential role in the immunomodulatory and inflammatory process, are involved in the acute inflammatory reaction post-TBI [8], [16], [71].

Thrombopoiesis process is regulated by thrombopoietin and other various inflammatory cytokines, such as IL-1, IL-3, IL-6, GM-CSF, and

TNF- $\alpha$  [72], [73]. Thrombopoietin is produced by the parenchymal and sinusoidal endothelial cells in the liver, and its production is increased in the presence of IL-6, which level also increased in the neuroinflammation processes post-TBI [45], [49], [74]. Platelets can also induce the release of inflammatory cytokines and interact with various cells, including neutrophils, macrophages, and T-lymphocytes, that will have an impact on the initiation or exacerbation of the inflammatory process [75], [76]. Therefore, the high number of platelets can reflect an increased release of inflammatory cytokines and platelet activation, which lead to increased inflammatory response and worsened SBI post-TBI [77].

Platelets play an active role in the inflammatory process [7]. Several other factors are also responsible for the platelet activation and the release of platelet's pro-inflammatory and prothrombotic molecules such as systemic inflammation and oxidative stress [78]. Inflammatory cells and bioactive molecules, such as IL-6 and CRP, can change the morphology and reactivity of platelets released from the bone marrow [79]. In the presence of stressor conditions, such as trauma, there is a positive correlation between thrombopoietin, ploidy from the platelet's progenitors, platelet's functional activity, and high platelet's count [80]. It is often seen in the inflammatory disorders, where an increased thrombopoiesis causes an increased number of platelets in the circulation, and a high number of very reactive large platelets migrate to the sites of inflammation [81].

A higher platelet's count can reflect the level of the ongoing inflammatory process and can also become a marker of the ongoing destructive inflammatory response and prothrombotic status, because of some inflammatory mediators can stimulate the proliferation of megakaryocytes, thus resulting in thrombocytosis [8]. A positive correlation was also found between the acute phase reactants and pro-inflammatory proteins (CRP, TNF- $\alpha$ , IL-1, and IL-6) with an increased platelet's count in the inflammatory conditions [82], [83]. Many studies about chronic inflammation from arthritis have found that there is an increase in platelets activation [84], [85]. The evidence of experimental and clinical researches also showed that there are some involvements of platelet-derived compounds in the inflammatory diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and other related thrombotic complication diseases [86], [87], [88].

In vascular diseases, such as atherosclerosis, platelets can interact with leukocytes and are considered as the central factor in the pathophysiology of vascular inflammation. The increased circulating platelet mass can be caused as a consequence of the presence of chronic inflammation. The activated platelets do not only produce growth factors such as platelet-derived growth factor and transforming growth factor- $\beta$  but also release chemokines that have an essential effect on the vascular inflammation, thus triggering thrombosis [89]. Platelets have intracellular thromboxane A<sub>2</sub> and

procoagulant surface proteins such as P-selectin and glycoprotein IIIa, so they have the potential to cause thrombosis if they are overactivated [90]. In addition, inflammation by itself can induce the occurrence of procoagulant processes and facilitate embolization, which is one of the leading causes of death [75].

### ***Lymphocyte's roles in traumatic injury***

In response to the physiological stresses, such as a traumatic injury, the body will release more cortisol hormone, which if the level is high, it can cause lymphopenia [91]. The higher the physiological stress level, the higher the cortisol level, thus, the lower the lymphocyte's count in the body. In contrast, the higher lymphocyte's count represents a more precise immune response and a more stable inflammatory pathway [92]. In cancer diseases, lymphocytes are responsible for the programmed cell death or apoptosis process [93]. Lymphocytes reflect a more controlled inflammatory pathway, and the lymphocytes-mediated apoptosis is less destructive to the surrounding cells compared to other models of cell death due to uncontrolled inflammation [8]. Therefore, the lower the lymphocyte's count post-TBI can reflect an increasingly destructive effect of the inflammatory response, which leads to a worsened SBI post-TBI.

### ***NLR***

NLR is a reflection of the degree of the inflammatory response (neutrophils) and immune status (lymphocytes), which shows an increase in the recruitment of inflammatory cells and the release of inflammatory cytokines when NLR level increases [94], [95]. Neutrophils are recruited into the site of injury in the brain within 1-h post-TBI and are able to release inflammatory mediators that can induce neuronal death and SBI [96], [97]. The increase in the peripheral neutrophils amount can increase the BBB damage, brain's tissue damage, and neuronal cell death, which then further aggravating the inflammatory reactions and brain tissue damage, thus increasing the severity of SBI [98].

NLR can be obtained from the CBC laboratory examination, is very easy to be measured, and can act as a predictor of clinical outcomes from cardiovascular diseases, stroke, and cancer [9], [10], [11]. Several studies have also found that high levels of NLR are associated with autoimmune diseases such as RA, SLE, psoriasis, ulcerative colitis, Sjogren's syndrome, and Behcet's disease [99], [100], [101], [102], [103].

A study found that a high NLR level in patients with spontaneous intracerebral hemorrhage (sICH) is significantly associated with the incidence of in-hospital mortality and mortality on the 90<sup>th</sup>-day [95]. It also found that the NLR level above 7.5 in patients with sICH had statistically significant potential for predicting the poor clinical outcomes (a Modified Rankin Scale from 3 to

6 was considered a poor outcome) and mortality [95]. Another study found that intracerebral hemorrhage patients with NLR level above 7.35 are associated with poor short-term survival (30-day mortality) and had a higher rate of intraventricular hemorrhage (hyperdense intraventricular signal not attributable to calcification or choroid plexus from computed tomography [CT]-scan images), ICH volume (from CT-scan images, calculated using ABC/2 formula), and lower GCS score compared to the intracerebral hemorrhage patients with NLR level 7.35 or lower [11]. In some other studies, they found that the NLR level can also be used as a prognostic factor to predict the clinical outcome (using Glasgow Outcome Scale/GOS score) and mortality of TBI patients in the 6<sup>th</sup>-month and 1<sup>st</sup>-year post-TBI, where a high NLR level is associated with poor clinical outcome (GOS score 1–3) in TBI patients [104], [105], [106]. Moreover, a study found that NLR is positively correlated with hs-CRP and ESR in patients with Takayasu's arteritis, which is an autoimmune inflammatory disease [7]. Thus, NLR has the potential and can be used as a promising inflammatory biomarker in predicting the severity of SBI post-TBI.

### ***PLR***

PLR can be used as a potential marker for determining the severity of an inflammatory reaction because platelets play an important role in the immunomodulatory and inflammatory processes [7], [71]. PLR is useful as a prognostic marker of the inflammatory response of several diseases such as intracranial hemorrhage, pulmonary embolism, cardiovascular diseases, cancer, and inflammatory diseases [77], [85], [107], [108], [109].

A study found that in intracranial hemorrhage patients, PLR is more superior in predicting the neurological outcome (using GCS at hospital discharge and Modified Rankin Scale at 6-month as the short-term and long-term neurological outcomes) and is more accurate in reflecting the severity of inflammatory reactions compared to the number of platelets or lymphocytes count alone [77], [110]. It also found that intracranial hemorrhage patients with a high PLR level, when admitted to the intensive care unit room, are significantly associated with a worse patient's GCS at hospital discharge [77]. Another study found that Takayasu's arteritis patients and patients with an active Takayasu's arteritis have a higher PLR level compared to the healthy patients and patients with Takayasu's arteritis in remission [7]. It also found that a high PLR level had been proved as an indicator of an increased inflammatory response associated with Takayasu's arteritis [7]. Moreover, it is also found that PLR is positively correlated with hs-CRP and ESR in patients with the autoimmune inflammatory Takayasu's arteritis disease [7]. Thus, PLR also has the potential and can act as an

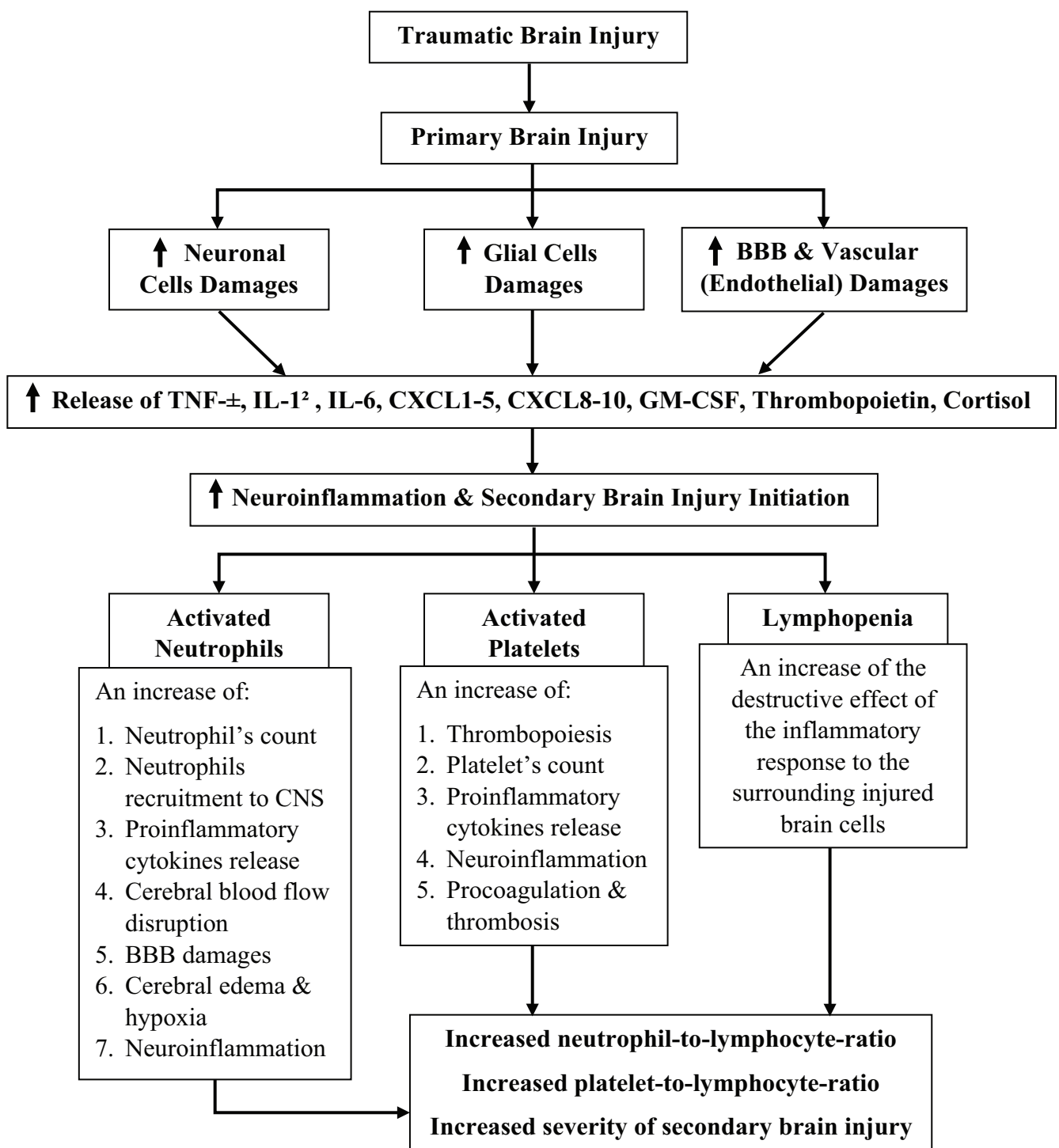


Figure 1: The mechanism of secondary brain injury involving the neutrophil's, platelet's, and lymphocyte's role

inflammatory biomarker in reflecting the severity of SBI in TBI patients.

## Summary

SBI is caused by the occurrence of the inflammatory cascades, immune system activity, and inflammation response post-TBI. Neutrophils, platelets,

and lymphocytes are involved in the SBI inflammatory reaction post-TBI. In the neuroinflammation process of the SBI, neutrophil's, and platelet's count will increase; meanwhile, the lymphocyte's count will decrease. These processes can increase the NLR and PLR level, which in turn indicate a higher neuroinflammation process, BBB damages, cerebral edema and hypoxia, and cellular damages (oxidative stress and apoptosis/necrosis of the neurons), so they have an impact on a higher severity level of the SBI process post-TBI post-TBI (Figure 1). Thus, the higher the NLR and PLR level,

the higher the severity level of the SBI. Further studies need to be done to provide more evidence about NLR and PLR in reflecting the severity of the SBI post-TBI.

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