Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2021 Oct 06; 9(F):574-583.
https://doi.org/10.3889/oamjms.2021.6985
eISSN: 1857-9655
Category: *F - Review Articles*
Section: *Narrative Review Article*

Role of Monocyte-to-lymphocyte Ratio, Mean Platelet Volume-to-Platelet Count Ratio, C-Reactive Protein and Erythrocyte Sedimentation Rate as Predictor of Severity in Secondary Traumatic Brain Injury: A Literature Review

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Edited by: Eli Djulejic
Citation: Natakusuma TISD, Mahadewa TGB, Mardhika PE, Maliawan S, Senapathi TGA, Ryalino C. Role of Monocyte-to-lymphocyte Ratio, Mean Platelet Volume-to-Platelet Count Ratio, C-Reactive Protein and Erythrocyte Sedimentation Rate as Predictor of Severity in Secondary Traumatic Brain Injury: A Literature Review. Open Access Maced J Med Sci. 2021 Oct 06; 9(F):574-583. https://doi.org/10.3889/oamjms.2021.6985
Keywords: C-reactive protein; Erythrocyte sedimentation rate; Inflammation; Mean platelet volume to platelet count ratio; Monocyte to lymphocyte ratio; Traumatic brain injury
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Received: 03-Aug-2021
Revised: 25-Sep-2021
Accepted: 26-Sep-2021

Funding: This research did not receive any financial support
Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: Secondary traumatic brain injury (TBI) is injury to the brain following primary TBI because of neuroinflammation as consequences of neuronal and glial cell injury which cause release of various inflammation cytokine and chemokine. Biomarker examination to predict the severity of secondary TBI is important to provide appropriate treatment to the patient. This article reviews possibility several common laboratory parameter such as monocyte-to-lymphocyte ratio (MLR), mean platelet volume-to-platelet count (PC) ratio (MPV-PCR), c-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) to predict severity of secondary TBI.

LITERATURE REVIEW: TBI activates microglia which increase infiltration and proliferation of monocyte. Neuroinflammation also increases thrombopoiesis which leads to increase megakaryocytes production. In the other hand, due to disruption of brain blood vessels because of trauma, coagulation cascade is also activated and leads to consumptive coagulopathy. These are reflected as high monocyte count, low PC, and high MPV. Lymphocyte count is reported low in TBI especially in poor outcome patients. CRP is an acute phase reactant that increased in inflammation condition. In TBI, increased production of Interleukin-6 leads to increase CRP production. In head injured patients, ESR level does not increase significantly in the acute phase of inflammation but last longer when compared to CRP.

CONCLUSION: MLR, MPV-PCR, CRP, and ESR could be predictor of severity in secondary TBI.

Background

Traumatic brain injury (TBI) is one of the main causes of mortality and morbidity in the world, which cause economic burden to the patients [1]. Decrease of cognitive and physical capabilities are suffered by the patient for a long time [2]. TBI is an injury to the brain and cranium which is caused by external mechanical forces and disrupts the structure and function of the brain [3]. Based on its pathophysiology, TBI is divided into primary and secondary TBI [4]. Primary TBI is injury that is caused directly by the mechanical forces to the brain tissue (axon, vascular, and glial cell). Secondary TBI is injury to the brain following primary TBI because of neuroinflammation as consequences of neuronal and glial cell injury which cause release of various inflammation cytokine and chemokine [5].

The process of secondary TBI is preventable and treatable. Secondary TBI is an important window of therapy and can determine prognosis of progression and recovery of TBI [5]. In this manner, appropriate initial management is required, including biomarker examination to predict the severity of secondary TBI. In this way, viability of the treatment could be improved and secondary TBI can be avoided.

Level of inflammatory cells and biomarkers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) can be used as indicator of increased systemic inflammatory response [6], [7]. However, CRP and ESR are not routinely performed in trauma patients despite its widely used in assessing

inflammatory disease. Complete blood count (CBC) is more routinely performed, easily available, and cheaper than CRP and ESR. In CBC, monocyte and platelet count (PC) can be obtained [8].

Secondary TBI

The pathophysiology of TBI is divided into primary and secondary TBI. Primary TBI occurs because of direct mechanical force on the head which causes damage to the integrity of brain cells. The trauma can be focal or diffuse due to stretching mechanism of brain structures [9], [10], [11]. Secondary TBI is injury that is occurred following primary injury. Secondary TBI is associated with inflammatory reactions, oxidative stress, neural excitotoxicity, impaired ion balance and massive release of neurotransmitters and mitochondrial dysfunction in the brain which can lead to progressive neuronal cell death [9], [12], [13].

Secondary TBI occurs within hours to days following primary TBI and worsens the injury that has already occurred. Secondary TBI develops mainly because of glial and neuronal cell dysfunction, metabolic disturbances, neuroinflammation, and brain swelling. All of these processes lead to various disturbances such as blood brain barrier (BBB) disruption, mitochondrial dysfunction, oxidative stress, and hypoperfusion to the brain tissue. Secondary TBI can have a more severe impact to the brain compared to primary TBI. However, secondary TBI is also a potential target in treating brain injury [14].

Following primary TBI, a severe inflammatory response is occurred. This process begins with the activation and migration of leukocytes around the damaged tissue. Activation of leukocytes causes pro-inflammatory mediators release such as cytokines interleukin (IL)-6, IL-1β, and chemokines released by microglia, immune cells, and neurons in surrounding tissues. All of these immune processes lead to astrogliosis. The presence of blood product and reactive oxygen species in extravascular space also initiates the inflammation [10], [15], [16].

The inflammatory response can exert a neuroprotective effect as well as exacerbating an already existing injury. The inflammatory response is important for clearing the damage effect of trauma and remodeling preparation. Long-lasting inflammatory processes can have neurotoxic effects, increase oxidative stress, apoptosis, and neuronal excitotoxicity [10], [17]. Activation of neuron due to brain injury can cause the release of various neuropeptides such as neurokinin A, neurokinin B, and substance P, which can cause neuroinflammation. The neuroinflammation increases leukocyte migration into the central nervous system environment, one of which is by expressing chemotactic effects on monocytes and neutrophils [10], [15].

The initiation of neuroinflammation following TBI is a complex process and involves many factors such as inflammatory cytokines and chemokines as well as anti-inflammatory factors [11]. The neuroinflammation that occurs is capable to regenerate and restore the tissue function. However, if it is activated excessively, it can cause further brain injury [18].

Role of Monocyte in Secondary TBI

Monocyte is a progenitor cell that has an important role in the pathophysiology of secondary TBI. Monocyte increases the concentration of macrophage in certain tissue. Monocyte is also considered could performed harmonization of immune processes that are occurred following trauma [19]. Macrophages, which are monocyte derivatives, are capable of producing growth factors and neuroprotective factors including IGF-1, BDNF, GDF15, vascular endothelial growth factor, and angiogenin [20]. Macrophages can trigger remodeling of damaged tissue and regeneration. However, excessive pro-inflammatory activity by macrophage in a long time can cause further injury to the affected tissue [15].

TBI activates microglia that leads to infiltration of neutrophils, lymphocytes and monocytes which will further differentiate into macrophages [11], [17]. Monocytes accumulate in the injured area up to 3 days after the onset of TBI and cause neurotrophic and neurotoxic effects [21], [22]. Activation of many pro-inflammatory cytokines attracts more immune cells and increases neuroinflammation following TBI. Monocytes in the injured area secretes pro-inflammatory cytokines such as IL-1-β, tumor necrosis factor (TNF)-α, IL-6, IL-8, and interferon-γ [23]. TNF-α and IL-1 are the initial pro-inflammatory cytokine released following trauma. Both of these cytokines are short-lived, 20 min and 6 min, respectively [24]. These pro-inflammatory cytokines stimulate other immune cells to induce secretion of other pro-inflammatory cytokines such as IL-6 and IL-8, and the anti-inflammatory cytokine IL-10 [25], [26].

Under normal conditions, the brain is considered an exclusive organ that is difficult to reach even by host immune system. The presence of the BBB makes it difficult for immune cells to infiltrate the brain. The BBB is formed by endothelial cells, tight junctions, pericytes, and astrocytes. It maintains homeostasis in the brain environment. The BBB prevents the neurotoxic components of plasma and blood cells. It also regulates the transport of various molecules, including circulating immune cells, in and out of the brain environment [11].

In brain injury, damage and dysfunction of the BBB can occur, causing plasma leakage and infiltration of blood cell components into the central nervous system [14], [27], [28]. The BBB disruption resulting from TBI allows monocytes to enter the

brain environment [19]. Monocytes begin to enter the perivascular space within 1–2 days after trauma, then differentiate into macrophages and persist for several weeks after trauma. CCL2 is a chemokine that attracts monocyte to infiltrate inflammation site. This chemokine is produced by epithelial cells of the choroid plexus following TBI [15].

One of the mechanisms of BBB disruption is an increase in aquaporin (AQP)1 and AQP4 regulations that can increase water transfer between cells [14]. Monocyte increases AQP4 expression which regulates extracellular fluid in the brain and reduced monocyte can cause disturbance in the process of resolution of vasogenic edema [20], [29]. Accumulation of fluid in intracellular or extracellular space in the brain leads to cerebral edema. Excessive cerebral edema leads to increase intracranial pressure because of limited intracranial cavity. Cerebral edema is an important pathology in head injury patients because it can disrupt perfusion and oxygenation to the brain, which eventually cause ischemic following TBI [30].

The neuroinflammation process triggers damage from BBB and infiltration of brain tissue by blood cells and edema and activation of immunocompetent cells and chemotactic factors. One of the most common pathological findings in this condition is the large number of leukocyte cells (monocytes and neutrophils). Leukocytes that invade BBB produce cytokines - good pro-inflammatory cytokines and do not participate in the BBB disruption process [31].

Monocyte plays an important role in maintaining permeability of BBB. Disruption of the BBB due to trauma causes BBB permeability disorders and its recovery is very dependent on microglia activity. Activation of microglia itself depends on peripheral macrophage. Therefore, increased monocytes as a macrophage progenitor become very important in the repairment process of BBB [32]. Macrophages are known to produce matricellular glycoprotein osteopontin which can induce extensions of astrocyte into the infarct area and contributes to the improvement of blood circulation [20].

Hypoxia can occur due to an imbalance between supply and demand for oxygen in certain tissues. Hypoxia is a common process in both acute and chronic inflammatory conditions. Monocytes can adapt well to a hypoxic environment. This can be done by converting oxidative metabolic processes into glycolysis [33]. Monocytes also increase proliferation in a hypoxic environment. Under a hypoxic environment, monocytes adapt by transcribing the HIF factor. One of the important responses in hypoxic tissues is angiogenesis, which occurs as a compensatory response to improved perfusion to these tissues. Macrophages have a major function in angiogenesis process where HIF-2a is the main mediator in the angiogenesis process [33]. Low levels of monocytes/macrophages can be correlated with the severity of the inflammatory process in ischemic brain lesions. Macrophages that infiltrate ischemic lesions are neuroprotective by increasing the anti-inflammatory response so as to prevent a prolonged inflammatory process [34].

Roles of Lymphocytes in Secondary Brain Injury

Hormone cortisol is released during high stress response such as traumatic injury. The high cortisol level in the body can lead to lymphopenia [35]. Uncontrolled inflammation increases level of stress, therefore increased level of cortisol and leads to the lower lymphocyte count. In the other hand, appropriate and stable immune response can be reflected by higher lymphocyte count [36]. Lymphocyte level is a reflection of a more controlled inflammation and less damage because of lymphocyte-mediated apoptosis [8]. Therefore, low lymphocyte count following TBI is a reflection of worsening or uncontrolled neuroinflammation that leads to worsening of secondary TBI.

Role of platelets in secondary brain injury

Thrombocytes have a major function in the process of inflammation [7]. Platelets can be a reflection of pro-inflammatory and prothrombotic conditions in the pathophysiological process of a disease [37]. Platelets can be classified as innate immune cells because in addition to functioning as hemostatic agents, platelets are also able to recognize pathogens and attract other immune cells such as neutrophils, macrophages, and lymphocytes to the affected site [38], [39]. Inflammation process through inflammatory cells and pro-inflammatory cytokine such as IL-6 has ability to deform the thrombocyte and increase the reactivity of thrombocyte [40].

Hemostasis or balancing of coagulation and anticoagulation is a dynamic process and thrombocytes have major function in hemostasis maintenance. Low activity of thrombocyte leads to disturbance of coagulation and eventually causes hypocoagulation and bleeding [41], [42]. Hemostasis is occurred following activation of platelets through adhesion, aggregation, and secretion phase. Adhesion is a process of platelet adhesion to injured endothelia. Shape change is occurred following platelet adhesion and leads to conformation changes in GPIIb-IIIa. Aggregation occurs due to conformational changes if GPIIb-IIIa which enhances the platelet plug formation. In secretion phase, thrombocyte releases granule which leads to increased P-selectin expression on its surface. Moreover, platelets also increase activation of coagulation cascade [43], [44].

Thrombocyte production (thrombopoiesis) is controlled by thrombopoietin and several inflammation mediators, such as IL-1, IL-3, IL-6, GM-CSF, and TNF-α [42], [45]. Thrombopoietin is produced in the liver by the parenchymal and sinusoidal endothelial cells [46], [47]. The inflammatory process that occurs in head injured patients can cause platelet activation and increase platelet production [31], [48]. Thrombopoietin is increased following TBI due to increased IL-6 because of neuroinflammation [46], [47], [49]. In trauma patients, thrombopoietin correlate positively with reactivity of platelet and increasing PC [50]. Thrombopoiesis during acute inflammation cause increasing production of large thrombocyte (megakaryocytes) which reflect as thrombocytosis in CBC [8]. Several inflammatory mediators have been identified that correlate with increased PC, which are CRP, TNF-α, IL-1, and IL-6 [51], [52].

Thrombopoiesis increase thrombocyte quantity in circulation in form of large and very reactive thrombocyte that attracted to the inflammation site [8], [53]. Active thrombocytes increase pro-inflammatory cytokine release and had effect to other inflammation cells such as neutrophils, macrophages, and T-lymphocytes [54], [55]. In addition, platelets also actively participate by playing a role in increasing the accumulation of leukocytes in inflamed tissues and assisting the process of leukocyte migration in blood vessel walls [38]. These processes initiate and cause worsening of neuroinflammation [54], [55].

Platelets themselves contribute to the inflammatory process through the arachidonic acid (AA) cascade [56]. Following trauma, the thrombocyte can be malfunction due to trauma-induced platelet dysfunction. Trauma-induced platelet dysfunction is a condition when platelets are not responding to its agonist. Activation of platelets can be achieved through several different pathways, including stimulation by adenosine diphosphate (ADP) and AA [57], [58]. ADP could activate thrombocyte directly while AA could activate thrombocytes indirectly. ADP directly binds to receptors such as P2Y1, P2Y12, and/or P2X1 on platelet membrane to activate thrombocyte. In the other hand, AA convert to thromboxane A_2 (TxA2) by the cyclooxygenase pathway before it can activate platelets. Increase in Ca^{2+} influx occurs after binding process between the agonist and its receptors. Platelets also deform to increase the surface, therefore, increase interactions between platelet and endothelial [59].

Following TBI, platelet has a temporary disturbed response to AA which is the characteristic of platelet dysfunction [60]. This finding explains longer bleeding time and tendency of oozing after TBI. This is a reflection of cyclooxygenase and thromboxane TxA2 receptor disturbance. This phenomenon is hypothetically caused by presence of unknown substance in plasma that inhibits platelet following TBI. Another possibility is hyperactivation of platelet in injured brain blood vessel leads to exhaustion and cause platelet to be in a refractory state [60]. In addition, inhibition of ADP is also a theory of platelet dysfunction in severe trauma [61]. Decreased ability of ADP to activate platelets is correlated with lower survival rate in TBI patients [62].

In severe trauma patients, there is increased activity of platelets. Risk of thrombosis is increases due to increased activity of platelet. Trauma activates coagulation cascade and generate thrombin which activates C5a complement system. Activation of the complement system further activates the response immune system following trauma [63]. Because of this mechanism, severe trauma leads to hypercoagulable state and increased immune response [41], [42]. Severe trauma can lead to activation of the protein C pathway which has antithrombotic and anti-inflammatory effects and eventually cause acute traumatic coagulopathy [64].

The brain contains high tissue factor (TF) which is a cofactor for factor VIIa in the extrinsic coagulation cascade [65], [66]. In TBI pathophysiology, TF is released following trauma and activate coagulation pathway [67], [68], [69]. Replacement of tissue thromboplastin activate extrinsic cascade to form fibrin clot [60], [70]. Furthermore, injured cerebrovascular structure activates thrombocyte because of endothelial disruption. Active thrombocytes activate intrinsic cascade to formed intravascular thrombosis due to vascular inflammation [60], [70]. It occurs because active platelet causes activation of TxA2 and procoagulant proteins such as P-selectin and glycoprotein IIA which can cause adhesion of platelet and cause thrombosis [71].

This phenomenon can overstimulated and consume platelets, rendering them desensitized to agonists for a time. Alternatively, thrombin degrades cyclooxygenase, an enzyme required for conversion of AA to TxA2 [72]. This leads to platelets being nonresponsive to AA stimulation. Overactivation of coagulation leads to consumptive coagulopathy and decreased of hyperactive platelet [73], [74]. In the other hand, to maintain the hemostasis balance, plasmin is activated and causing fibrinolysis and clot lysis [60].

Yolcu *et al*. found association between trauma severity and level of platelet [25]. Other study by Jacoby *et al*. reported that activation of platelet and its function is usually occurred following severe injury. Increased activation of platelet combines with decreased of its major function was reported associate with increased mortality [75], [76].

Monocyte-to-Lymphocyte Ratio (MLR)

Monocyte count is a reflection of innate immunity while lymphocyte count is a reflection of

adaptive immunity. Therefore, MLR is an indicator of immunity balance between innate and adaptive immunity. The magnitude of neuroinflammation can be reflected in MLR value, whereas higher MLR reflect more severe secondary injury.

MLR is a fairly new parameter to be used as a marker of inflammatory response. MLR itself has been proven to be accurate as a factor in the severity and prognosis of various diseases such as tuberculosis and coronary heart disease [77], [78]. Jan *et al*. also found that MLR can be used as a prognostic factor for malignancy [78]. Sheng *et al*. suggested that MLR is a predictor of the inflammatory process and the risk of hematoma expansion in cases of cerebral contusion after brain injury [79]. In stroke patients, MLR was reported associated with depression occurrence within 3 months [80].

Mean Platelet Volume-to-PC Ratio (MPV-PCR)

The MPV is a laboratory parameter that showing function and activation of platelet [42], [81]. The MPV is showing average size of thrombocytes in plasma which ranging between 9.7 and 12.8 fl typically. The MPV can be increased because of presence of larger and hyperactive thrombocytes from spleen. The MPV can also decreased mainly because of consumption of larger and more brittle thrombocytes [82], [83].

The MPV has been considered as inflammation marker and widely used to assess inflammation in inflammatory bowel disease, asthma, and chronic obstructive pulmonary disease [84], [85], [86]. MPV is considered as marker of inflammation in trauma patients [25]. Lippi *et al.* reported severity of mild head trauma was associate parallelly with the lower MPV [82].

MPV is an indicator of inflammation and prothrombotic conditions because thrombopoiesis is regulated by thrombopoietin and several pro-inflammatory cytokines (IL-1, IL-6, and TNF-α) [42]. In addition to their function in hemostasis, platelets can amplify the inflammation response that occurs in various diseases [84]. The function of thrombocyte is determined by its size and age. Larger thrombocytes are considered younger, more active, and aggregable than the smaller ones [25], [87]. Larger thrombocytes contain more granules and produce more TxA2. They also secrete more serotonin and β-thromboglobulin [25]. The volume of platelet can be interfered by cytokines and acute phase reactant. Megakaryopoiesis process can be inhibited by accumulation of pro-inflammation cytokine and acute-phase reactants. The inhibited megakaryopoiesis causes release of small volume platelet to the circulation [25]. In acute inflammation, large platelet is required due to its ability to release pro-inflammatory cytokines and thrombotic agents. They are also more active compare do smaller one [25], [42]. Lippi *et al.* reported severity of mild head trauma was associated parallelly with lower MPV [82]. MPV is considered as marker of inflammation in trauma patients [25].

PC itself was found to be reduced in various severe diseases such as heart infarction and various liver diseases such as liver cirrhosis [88]. The increase in MPV was found to be inversely proportional to PC levels, so that the increase in the ratio of MPV and PC was considered to describe the severity of a particular disease, one of which was in cases of deep vein thrombosis [81].

Thrombocytopenia is one of predictor of mortality in severe TBI [89]. PC was reported low in TBI and more reduced at day 3 post-trauma [60], [90]. Lippi *et al.* reported patients with mild TBI exhibit lower PC that is accompanied by lesser MPV [82]. Cortiana *et al*. reported that average platelet number remained low for 5 days following onset of TBI and began to increase on day 6th [91]. Auer also reported that thrombocytopenia occurs within 1 week in TBI patients and more decreased in non-survivors [92].

Regarding role of MPV-PC ratio to CNS condition, Ray *et al*. reported that MPV-PC ratio can predict delayed cerebral ischemia occurrence following spontaneous subarachnoid hemorrhage. The occurrence of delayed cerebral ischemia was thought as result of platelet associated thrombogenicity [93]. Based on what have been described, MPV-PC ratio is a parameter of thrombosis event following primary TBI, beside indicator of neuroinflammation. The thrombosis event following TBI is considered as secondary insult that can cause more severe secondary TBI.

CRP

CRP is an acute phase reactant that synthesize in liver [94]. It is part of pentraxin family of calcium-dependent ligand-binding plasma proteins, which activate the classic complement pathway. They bind to the phosphocholine that is expressed on the surface of dead or dying cells to activate complement pathway [95], [96]. CRP production is stimulated by several factors such as infection, inflammation, stress response, tissue necrosis, trauma, and malignancy [97], [98]. While CRP is produced primarily by hepatocytes, it can be generated by human neurons [99]. CRP synthesis is induced mainly by IL-6 and increased by IL-1β and TNF-α [100], [101].

Severe TBI cause neuroinflammation which is indicated by activation of microglia and astrocyte, disruption of BBB and increase of pro-inflammatory cytokine, which are IL-1, IL-6, and TNF-α. It eventually resulted in neuron damage. The damage of neuron increases production of IL-6 which stimulate production of CRP in liver [102]. CRP is elevated in the first 2 weeks after TBI, proportional to the severity of systemic injury and more so in subjects with intracranial lesions on CT or MRI scans [103].

Increased of CRP is proven as predictor of poor outcome in head injured patients whereas higher CRP indicate more severe secondary TBI [104]. CRP level was also reported associated with level of consciousness assessed by GCS score [105]. Bomba *et al*. reported that CRP is possible to be used as predictor of SIRS in severe TBI which predict poor prognosis [102]. Intensive care length of stay and mechanical ventilation duration was associated with level of CRP [106], [107]. Traumatic SAH volume and presence of vasospasm induced a significant CRP response [105], [108], [109]. The presence of blood and higher clot volume was associated with increased CRP [99]. Prognostically, CRP measured through the first 2 weeks post-injury was significantly higher in subjects with poorer outcome (death or severe disability) compared to favorable outcome (GOSE > 5) at 6 months [103].

ESR

The ESR is a laboratory parameter that indicates the rate of erythrocyte sedimentation or settle in the plasma from blood specimens that has been given anti coagulation in a period of time (usually 60 min), so they have units of millimeters (mm) per hour [110]. The rate of erythrocyte sedimentation in plasma is influenced by the levels of acute-phase reactant proteins. Therefore, ESR is used to assess the acute-phase response to an inflammation process [111].

Various inflammation biomarkers that are more sensitive and specific have been found. However, ESR still can be used in assessing various diseases such as autoimmune diseases as the basis for diagnostic criteria [111]. Despite its sensitivity and specificity, ESR has been widely used mainly because of its simplicity, inexpensive, and familiarity to many practitioners [112]. ESR is reported increase in acute ischemic stroke and reflected the severity of local brain damage [113]. In head injured patients, ESR level does not increase significantly in the acute phase of inflammation but last longer when compared to CRP which is other acute-phase reactant protein [48]. It also a parameter of thrombosis event following primary TBI which is considered as secondary insult that can cause more severe secondary TBI.

Conclusion

Increased monocyte count and platelet volume followed by decreased lymphocyte and PC are reflection of neuroinflammation severity following TBI. High level of CRP and high ESR are also indicator of inflammation severity following TBI. Therefore, MLR, MPV-PCR, CRP, and ESR could be predictor of severity in secondary TBI.

Author Contribution

All authors contribute equally in the making process of this article.

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