# LITERATURE REVIEW: THE ROLE OF CSF-BLOOD ALBUMIN RATIO IN DETERMINE SEVERITY OF TRAUMATIC BRAIN INJURY

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**Abstract:**
Traumatic brain injury (TBI) continues to be a global burden. Due to its complex pathophysiology and limited knowledge of its severity, mortality, and morbidity remain relatively high. The Glasgow Coma Scale (GCS) has been used for almost fifty years to determine the severity of TBI, but its use has recently been questioned. Blood and cerebrospinal fluid biomarkers have been studied to determine the severity of TBI cases. The CSF-blood ratio of albumin levels could be one option to determine TBI severity, this ratio could determine BBB integrity. BBB disruption was one of the pathophysiology that could cause cerebral edema and altered blood flow that will worsen its outcome. Recent studies showed that BBB integrity play a pivotal role in TBI pathophysiology, influencing GCS score and patient outcome. Therefore, the CSF-blood albumin ratio could be used to determine the severity of TBI but further studies are needed to confirm this finding.

**Keywords**: Blood-Cerebrospinal Fluid Albumin Ratio, Glasgow Coma Scale, Traumatic Brain Injury

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## INTRODUCTION

Traumatic Brain Injury (TBI) has become a global health concern due to its high mortality rates, long-term disabilities, and socio-economic burden. Besides impacting the quality of life for patients, TBI also affects interpersonal, social, and occupational functions, leading to financial burdens for both families and communities (CDC, 2015). The incidence and severity of TBI vary significantly worldwide. In Indonesia, it is estimated that there are approximately 500,000 cases of head injuries annually (Fitriana, 2018). The Basic Health Research results in 2013 showed that 100,000 lives were lost due to head injuries (Kementerian Kesehatan RI, 2013). According to the 2018 Basic Health Research report (Riset Kesehatan Dasar, 2018), head injuries were the third most common injuries, accounting for 11.9% of cases, following injuries to the lower limbs and upper limbs. The prevalence of head injuries in the province of Bali was 10.7%, with the highest prevalence in the province of Gorontalo at 17.9% (Ministry of Health of the Republic of Indonesia, 2019). In 2022, RSUD Dr. Soetomo recorded about 200 cases of traumatic brain injury each month.

Glasgow coma scale (GCS) has been used, for almost 50 years since its first introduced, to determine brain disfunction and severity in traumatic brain injury (Matis&Theodossios,2008). However, these methods have some minor problems in determine severity of GCS such as risk of delayed the care of the patients, weak to predict patient outcome and has a high inter-rater reliability (Fitzgerald et al, 2022; Chawla et al, 2020). TBI has a very complex pathophysiology, especially severe TBI, therefore determining severity of TBI only using GCS was unreasonable.

Blood-Brain-Barrier (BBB) dysfunction is one of the factors that determines severity of TBI and often occurs in severe TBI which increased the risk patient mortality and morbidity (Ng & Lee, 2019). An impaired BBB could be detected due to the leakage of serum albumin into the extracellular space that leads to exacerbating brain edema. Assessing BBB permeability by measuring ratio of albumin in cerebrospinal fluid (CSF) and serum is crucial in central nervous system disorders (Jeffcote & Ho, 2010). Some studies showed that there is a correlation between mean daily intracranial pressure, blood albumin and CSF albumin in neurotrauma patients following severe TBI showing that there are BBB dysfunction and vasogenic edema that contribute to brain edema (Agarwal et al, 2020;

Jeffcote & Ho, 2010).

This literature review will show some topics about the role of CSF-blood albumin ratio in determine severity of traumatic brain injury.

## METHODOLOGY

The methodology comprised a literature review, encompassing database searches, inclusion criteria, data extraction and quality assessment, ultimately resulting in a comprehensive exploration of the CSF to blood albumin ratio and GCS scores in TBI patients..

## OVERVIEW LITERATURE

### Traumatic Brain Injury (TBI)

Traumatic Brain Injury (TBI) is a disruption of normal brain function caused by sudden and severe external mechanical forces (such as blows, impacts, or jolts) (Agarwal et al., 2020; Pervez et al., 2018). This can occur when someone is struck by an object or when an object penetrates the head and enters the brain tissue, causing temporary or permanent damage (Tahir & Shuja, 2011).

Globally, TBI is a leading cause of death in young adults and a significant cause of mortality and disability worldwide. A study by Dewan et al estimated that approximately 69 million people suffer TBI from all causes each year, with more than 7% suffering severe TBI based on GCS, AIS, and other traumatic injury severity scores (Dewan et al., 2018). Data from the Centers for Disease Control and Prevention (CDC) in 2014 indicated that TBI contributed to nearly 3 million emergency department visits, hospitalizations, and deaths in over 54.000 adults and 2.500 children (CDC, 2014).

TBI can be categorized into two categories based on its pathophysiology: primary injury and secondary injury (Ng & Lee, 2019)

a) Primary Injury

Primary brain injury occurs when external forces cause local or diffuse brain damage (Saleh & Rehatta, 2023). This injury triggers a cascade of events, including potassium release, membrane depolarization, and leading to the release of amino acids and excitatory neurotransmitters. After the brain injury occurs, axonal membrane damage occurs, followed by the release of potassium ions from the cells, leading to membrane depolarization. This condition results in depolarization, leading to the release of amino acids and excitatory neurotransmitters.

Calcium ions continue to enter, and potassium ions continue to exit, causing intracellular calcium levels to rise, disrupting intracellular function and leading to cellular hypoxia. When hypoxia occurs, and the brain is forced to undergo glycolytic metabolism, lactic acid accumulates. This accumulation of lactic acid then damages the blood-brain barrier and causes cell death. This triggers a local inflammatory response that typically occurs 4-6 hours after the initial injury. This inflammatory response can lead to diffuse damage through the release of neurotransmitters that flood the brain (Capizzi et al., 2020).

b) Secondary Injury

Secondary brain injury results from a progressive pathological process following complex primary injuries that begin after the primary injury with a slow onset of clinical presentation (Saleh & Rehatta, 2023). It can result from disrupted biochemical, cellular, and physiological processes triggered by the primary injury. Secondary brain injury can occur due to intracranial processes (intracranial secondary insult) such as intracranial bleeding, ischemia, cerebral edema, hematoma, increased intracranial pressure, decreased cerebral perfusion pressure, vasospasm, and inflammation. Secondary brain injury can also occur due to extracranial or systemic processes (systemic secondary insult) such as hypotension, hypoxia, hypercapnia, hypocapnia, and imbalances (Santoso et al., 2016).

The increase in intracranial pressure that occurs in TBI can lead to a decrease in cerebral perfusion pressure. This can happen because of increased blood pressure as a compensation for the increased intracranial pressure, thus maintaining a constant cerebral perfusion pressure. However, excessive increases can lead to an unstable cerebral perfusion pressure. A study conducted in the emergency department of Dr. Soetomo Hospital showed that 94.6% of severe TBI patients experienced autoregulatory compensation in the brain, maintaining a constant cerebral perfusion pressure, with a Mean Arterial Perfusion (MAP) range between 60-100 mmHg (Hutauruk et al., 2020).

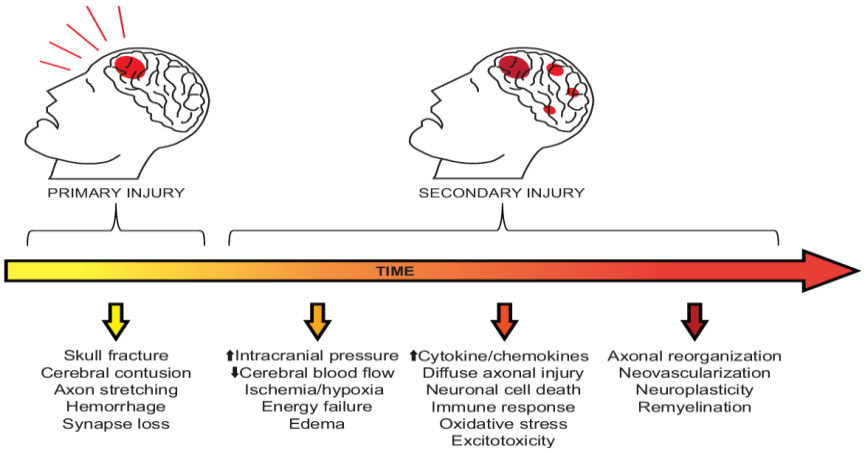


Figure (1) Primary and secondary injuries after TBI
Source: (Agarwal et al., 2020)

There are several factors that can contribute to the occurrence of secondary injury, including excitotoxicity, mitochondrial dysfunction, oxidative stress, lipid peroxidation, neuroinflammation, axonal degeneration, and cell apoptosis.

The severity of TBI can be determined using the GCS. TBI can be categorized into three groups (based on GCS), namely mild TBI if GCS is 13-15, moderate TBI if GCS is 9-12, and severe TBI if GCS is 3-8. GCS is used fneuor assessment because the method is simple and easy to understand. GCS is measured by assessing eye, verbal, and motor responses (Matis & Birbilis, 2008; Padmaja et al., 2017). GCS can not only be used to measure the severity of TBI but can also be used to assess therapy response, evaluation, and prognosis. However, GCS has weaknesses, making it difficult or impossible to assess the severity and evaluation of TBI, particularly in patients who are intubated, using sedation or muscle paralysis, and have a history of alcohol use (Stefanović et al., 2017).

Table (1) Classification of TBI severity

| Criteria of TBI Severity | | | |
|---|---|---|---|
| Glasgow coma scale | 13 – 15 | 9 - 12 | ≤ 8 |
| Loss of consciousness | 0 – 30 min | 30 min to 24 h | More than 24 h |
| Post-traumatic amnesia | Less than 24 h or none | More than 24 h less than 1 week | More than 1 week |
| Alteration of consciousness/mental state | A moment up to 24 h | > 24 h, severity based on other criteria | > 24 h, severity based on other criteria |

Source: (Rapp et al., 2013)

Recently, several studies have demonstrated the role of blood and CSF biomarkers in determining prognosis to prevent long-term neurological sequelae in TBI patients. These biomarkers could help to differentiate the severity of TBI based on neuronal damage, such as axonal injury (total tau protein and neurofilament light polypeptide), neuronal injury (non-specific enolase) and astroglial injury (S100b, glial fibrillary acidic protein). The CSF is closely linked to the brain's extracellular matrix, and its composition reflects the biochemical changes occurring within this organ. Consequently, CSF analysis can provide valuable biomarkers for assessing brain injuries (Zetterberg.2013).

**Blood-Brain Barrier (BBB) and Cerebrospinal Fluid (CSF) physiology**

The BBB was discovered in the late 19th century when German physician Paul Ehrlich injected a dye into the bloodstream of rats. The dye infiltrated all tissues except the brain and spinal cord, demonstrating the presence of a barrier between the brain and blood (Woodruff, 2022). The BBB itself is a highly selective, semipermeable membrane located between the blood

and the interstitium of the brain. This unique barrier allows the cerebral vasculature to regulate the movement of molecules and ions between the blood and the brain (Daneman & Prat, 2015). The BBB consists of endothelial cells (ECs) of the cerebral capillary wall that are held together through tight junctions (TJs). These TJs are surrounded by pericytes, astrocytes, and basal lamina, all of which contribute to the highly selective nature of the BBB, restricting the flow of substances from the blood to the brain more than other capillaries in the body. The BBB controls the entry of molecules from the plasma into the CNS (Dong, 2018).

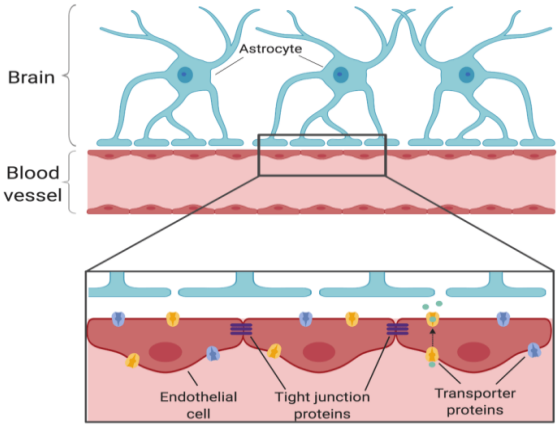


Figure (2) The BBB consists of ECs tightly connected to each other by TJ proteins (purple). These tight protein interactions prevent unwanted substances from flowing between the blood and the brain. Various types of transporter proteins (yellow & blue) only transport specific types of molecules between the blood and the brain

Source: (BioRender.com; 2019)

The BBB is a critical component of the neurovascular unit (NVU), characterized by TJs between ECs. The NVU is primarily located within the capillaries and post-capillary venules that supply blood to the CNS, encompassing most of the brain and spinal cord. However, there is an exception in the form of specialized neuroepithelial structures within the CNS known as circumventricular organs (CVOs). In contrast to the rest of the CNS, CVOs are vascularized by fenestrated capillaries, allowing for bidirectional communication between the blood and the brain. These CVOs are clustered along the midline of the brain, proximal to the third and fourth ventricles. Seven CVOs serve specific functions and are divided into secretory and sensory organs. The four secretory CVOs include the median eminence, neurohypophysis, pineal gland, and sub-commissural organ, while the three sensory CVOs consist of the area postrema, subfornical organ, and organum vasculosum of the lamina terminalis (Kaur & Ling, 2017).

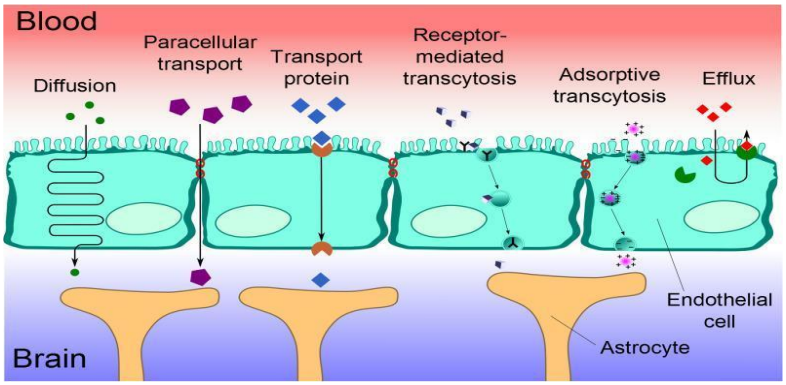


Figure (3) Transport Process Inside the BBB
Source: (Gawdi et al., 2022)

The BBB is formed by a single layer of endothelial cells in brain capillaries connected by tight junctions (zonula occludens). These tight junctions regulate the transport of molecules between the blood and the central nervous system (CNS). The BBB effectively prevents the diffusion of most water-soluble molecules above 500 Da (Blyth et al., 2009). Serum albumin constitutes approximately 50% of the proteins in plasma. It is a heart-shaped protein with a molecular weight of about 66.4 kDa. Serum albumin serves various functions as a major plasma component, affecting oncotic pressure, transporting fatty acids, carrying certain hormones, influencing drug pharmacokinetics, binding metals and heme, and acting as an antioxidant (LeVine, 2016). Proteins can traverse the BBB into the CNS at different rates, depending on their hydrodynamic radius, with larger proteins experiencing more restricted movement than smaller ones. This limitation affects the transport of albumin into the CNS. A damaged and exposed BBB can aid in the diagnosis of brain injury and facilitate pharmacological treatments (Skillbäck et al., 2017). Thus, functional assessment of the BBB by CSF and blood albumin calculation is widely accepted as the gold standard for assessing BBB permeability. Albumin can be an optimal candidate for measurement of BBB function or integrity because it is synthesized peripherally, is not catabolized in the CNS, and does not easily diffuse past an intact BBB (Skillbäck et al., 2017).

Peripheral capillary ECs consist of numerous TJs, possess fewer cytoplasmic vesicles, and have a higher concentration of mitochondria. These TJs restrict paracellular movement and divide the EC membrane into two distinct sides with different membrane compositions. To overcome the limitation of solute movement, several transport pathways facilitate molecular movement across the BBB (Kaur & Ling, 2017):

1. Diffusion of substances into the brain is achieved through the paracellular or transcellular pathway. Small water-soluble molecules can traverse the TJs of the BBB via simple diffusion. Small fat-soluble substances, such as alcohol or steroid hormones, can transcellularly penetrate the BBB through the dissolution of its lipid plasma membrane. Other substances, including glucose and amino acids, require specialized transport routes to cross the BBB.
2. Protein transport is necessary for certain solutes, such as glucose or amino acids, to cross the BBB. These solutes bind to protein transporters on one side of the membrane, triggering protein changes and subsequent substance transport from areas of high to low concentrations. In the case of charged compounds moving against the concentration gradient, ATP is utilized for this process (Y. Chen & Liu, 2012).
3. Efflux pumps are responsible for removing endogenous and exogenous compounds, such as drugs, from the brain into the blood. Efflux pumps actively transport drugs from the ATP-binding cassette (ABC) as the primary distributor of active drugs and eliminate them from the CNS. This mechanism can be an obstacle, as it may limit the distribution of drugs beneficial for treating CNS diseases (Löscher & Potschka, 2005).
4. Receptor-Mediated Transcytosis (RMT) enables the selective uptake of macromolecules. Brain ECs possess receptors for specific molecules, including insulin receptors, transferrin receptors, and lipoprotein transport receptors. Selective molecules bind to their receptors in clathrin-coated pits, specialized areas of the plasma membrane. These pits then enter the cytoplasm and break free to form coated vesicles. The ligand can dissociate from the receptor once endosomal acidification is complete, allowing it to cross to the other side of the membrane (Pulgar, 2019).
5. Adsorptive-mediated transcytosis (AMT), also known as pinocytosis, is triggered by the interaction between positively charged proteins and the negatively charged surface of the plasma membrane. Cationic molecules can bind to the luminal surface of endothelial cells and subsequently undergo exocytosis on the abluminal surface. The high content of mitochondria in cerebral endothelial cells provides the necessary means for molecules to move through the endothelial cytoplasm (Hervé et al., 2008).
6. Cell-mediated transcytosis (CMT) is a mechanism of pathogen entry into the brain through a "Trojan horse" model, which utilizes immune cells such as macrophages and monocytes to traverse the BBB. CMT can be used for all types of molecules to cross the BBB (Lorin et al., 2020).

One important function of the BBB is to maintain brain homeostasis, achieved through tightly regulated transport of ions and solutes between intravascular plasma and the CNS via molecular exchange pathways that facilitate the movement of molecules from the blood to the brain and vice versa. However, not all molecules require a transport mechanism across the BBB. Gases such as carbon dioxide and oxygen, as well as lipophilic molecules with molecular weights below 400 Da, can freely diffuse across the BBB (Zeisel et al., 2015).

**Cerebrospinal Fluid (CSF)**

Cerebrospinal Fluid (CSF) is an ultrafiltrate of plasma found within the ventricles of the brain and the subarachnoid space of the head and spine (Sakka et al., 2011). CSF serves essential functions, including

nourishing, waste removal, and brain protection (Spector et al., 2015). The estimated volume of adult CSF is approximately 150 ml, distributed as 125 ml in the subarachnoid space and 25 ml in the ventricles. The choroid plexus primarily secretes CSF, with a constant secretion rate that allows for CSF renewal approximately 4-5 times per 24 hours in young adults (Sakka et al., 2011). CSF is continuously secreted with an unchanged composition (Sakka et al., 2011).

CSF is secreted by the choroid plexus (CP) located within the brain's ventricles, with the lateral ventricles being the primary producers. It flows through the ventricular system in a rostral to caudal direction. CSF produced in the lateral ventricles travels through the interventricular foramen into the third ventricle, passes through the cerebral aqueduct into the fourth ventricle, and then proceeds through the median aperture (also known as the foramen of Magendie) into the subarachnoid space at the brain's base. CSF travels over the brain's surface and down the spinal cord's length while within the subarachnoid space. It exits the subarachnoid space through arachnoid villi located along the superior sagittal venous sinus, intracranial venous sinus, and around the spinal nerve roots. Arachnoid villi are protrusions of the arachnoid mater through the dura mater into the venous sinus lumen. A pressure gradient facilitates its absorption (Cash & Theus, 2020; Sakka et al., 2011).

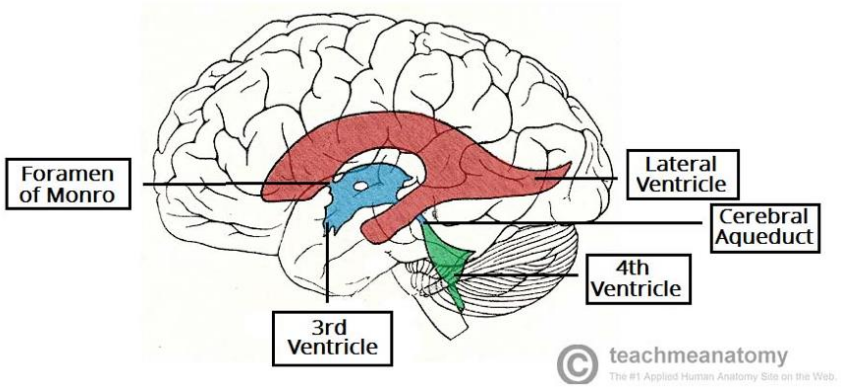


Figure (4) Anatomy of the ventricular system
Source: (TeachMeSurgery.com, 2020)

CSF serves hydromechanical protection for the neuroaxis through two mechanisms. Firstly, it acts as a shock absorber, cushioning the brain from external pressure. Secondly, CSF renders the brain and spinal cord buoyant, reducing the effective weight of the brain from its normal 1.500 grams to 50 grams. This reduction in weight minimizes the force applied to the brain parenchyma and cerebral vessels during mechanical injury.

Another function of CSF is to maintain the homeostasis of brain interstitial fluid. CSF also assists in removing metabolic waste products from the brain, such as peroxidation products, glycosylated proteins, excess neurotransmitters, debris from the ventricular lining, bacteria, viruses, and unnecessary molecules. The accumulation of such unnecessary molecules, observed in aging and certain neurodegenerative diseases, impairs neuronal function in the brain. The primary nutrient supply for the brain is through the CP-CSF-ECSB nexus. Substrates required by the brain are transported from the blood, through the CP, into the CSF, and then diffuse into the extracellular space of the brain (ECSB) to be utilized by specific brain cells as needed (Damkier et al., 2010; Spector et al., 2015).

**BBB dysfunction in TBI**

BBB dysfunction can be observed in various chronic degenerative neurological disorders, such as Alzheimer's disease, amyotrophic lateral sclerosis (ALS), multiple sclerosis, Parkinson's disease, as well as acute CNS disorders like TBI and stroke. BBB disruption associated with TBI is considered a major risk factor for high morbidity and mortality. The primary consequence of BBB disruption in TBI is cerebral edema due to the accumulation of excess fluid in the brain. There are two types of edema: cytotoxic and vasogenic. Vasogenic edema results from fluid accumulation in the perivascular space, causing changes in cerebral blood flow (CBF) and increased intracranial pressure (ICP). Cytotoxic edema is caused by the activation of ion channels that promote water entry into the intracellular space of various cell types, resulting in further disruption of the BBB. Without immediate intervention, increased ICP and altered CBF can lead to irreversible tissue damage and cell death, contributing

to high mortality in severe cases of TBI (Cash & Theus, 2020). Vasogenic edema results from fluid accumulation in the perivascular space, causing changes in CBF and increased ICP.

There is an association between the CSF and blood albumin ratio and TBI according to the underlying pathophysiology. An abnormal CSF and blood albumin ratio represents a deviation from the normal range of albumin concentration in CSF compared to serum albumin concentration. This ratio serves as an indicator of the integrity of the BBB. An increase in the ratio signifies a disruption in BBB integrity, leading to albumin leakage into the CSF (Human Phenotype Ontology, 2022).

The CSF and blood albumin ratio is a widely employed biomarker for evaluating BBB integrity in various neurological conditions. Clinical laboratories routinely conduct CSF analyses, including measurements of albumin and total protein (Sofronescu, 2016). Vascular leakage in the brain eventually results in an elevated CSF-to-blood albumin ratio due to the release of albumin into the brain's interstitial fluid (Zetterberg et al., 2010). Nonetheless, in most individuals with TBI, the BBB remains intact, limiting the applicability of such biomarkers (Sofronescu, 2016).

There are two studies that demonstrate an increase in the ratio of CSF to blood albumin levels in patients with severe TBI related to the neuroinflammatory response. However, other studies indicate no change in this ratio value in patients with mild TBI, suggesting that in mild conditions, the integrity of the BBB remains intact (Zetterberg et al., 2010). Although the CSF-blood albumin ratio is the current gold standard for assessing BW integrity, studies have shown that several complement proteins are significantly positively correlated with CSF-blood albumin ratio values (Lindblad et al., 2021). These novel findings could be used as prognostic markers for severe TBI. There are several mechanisms that explain the decrease in serum albumin levels in patients with TBI. Firstly, albumin consumption increases during stressful conditions. Secondly, bleeding can lead to albumin loss. Thirdly, inadequate dietary intake and suppression of hepatic function result in reduced albumin synthesis. Additionally, dysfunction of the BBB and increased vascular permeability can also cause albumin to extravasate. When the integrity of the BBB is compromised in TBI patients, infiltration is one of the factors contributing to decreased albumin levels (D. Chen et al., 2014).

Table (2) TBI Biomarker Interval Reference

| **Variable** | **Reference Interval** |
|---|---|
| $Albumin_{CSF}$ (mg/L) | 15 - 29 years: < 260 |
| | ≥ 50 years: < 400 |
| $Albumin_{blood}$ (g/L) | < 41 years: 36 - 48 |
| | ≥ 71 years: 34 - 45 |
| $Q_A$ (no unit) | 15 - 29 years: $< 6 \times 10^{-3}$ |
| | ≥ 50 years: $< 9 \times 10^{-3}$ |

Nb: $Q_A$: Blood albumin quotient.
Source: (Kaplan & Pesce, 2010; Lindblad et al., 2020)

At the microscopic level, peripheral blood vessels consist of nonfenestrated capillaries, comprising a continuous basement membrane and a single layer of endothelial cells with intercellular "gaps." These gaps are filled by the endothelial glycocalyx, which allows fluid and electrolytes to pass through but not larger proteins. This arrangement results in the subendothelial glycocalyx space, considered the intravascular space, being relatively devoid of proteins. However, proteins can enter the interstitial space through endocytosis and exocytosis. Consequently, the albumin content in the interstitial and intravascular spaces is relatively equal, while the subendothelial glycocalyx space contains minimal albumin. As a result, the transcapillary membrane pressure gradient is primarily determined by hydrostatic pressure and plasma oncotic pressure, which, in turn, is significantly influenced by serum albumin, in accordance with Starling's principle.

In contrast, in an intact BBB, where only water (but not electrolytes and albumin) can move freely between the two compartments due to epithelial tight junctions, the transcapillary membrane pressure gradient is solely determined by serum osmolality. Therefore, with an intact BBB, changes in albumin concentration and associated variations in plasma oncotic pressure would theoretically have little impact on brain output, as long as serum osmolality remains unchanged.

However, when the BBB is disrupted, as in cerebral diseases involving tumors, trauma, ischemic events, or hemorrhagic transformations, the movement of most

large proteins, ions, and transcapillary fluxes of solutes is likely to occur in a straightforward manner dependent on the concentration of brain extracellular fluid and neuronal intracellular space. Without the protective barrier of an intact BBB and with the loss of endothelial tight-junction integrity, there is the potential for clinically significant cerebral edema (Ma & Bebawy, 2021).

In normal individuals, the main source of CSF albumin is transport from the blood, via glycoprotein receptors that bind to epithelial cells in the choroid plexus, and are subsequently transferred to the ventricular CSF (LeVine, 2016).

Albumin constitutes two-thirds of total plasma protein, contributing about 80% of the plasma colloid osmotic pressure and playing a crucial role in the transport and binding of many molecules. There are several possible causes of hypoalbuminemia upon admission in TBI. Firstly, the loss of serum albumin in TBI can be attributed to bleeding. Trauma causes damage to blood vessels, including the blood-brain barrier, leading to the loss of albumin. Secondly, intense stress after TBI can also result in a massive release of inflammatory mediators that increase vascular permeability (Luo et al., 2019). Thirdly, inadequate intake and depressed liver function can reduce albumin synthesis. Additionally, albumin extravasation occurs due to increased vascular permeability and BBB dysfunction. When BBB integrity is compromised in patients with TBI, infiltration is one of the mechanisms resulting in albumin reduction. Furthermore, albumin serves many other important physiological functions. Lower albumin levels are likely to weaken the patient's endurance, leading to slow wound healing and reduced resistance to secondary infections (D. Chen et al., 2014).

Research on the topic of TBI suggests that serum albumin can serve as a biomarker to predict the prognosis of patients with TBI. Rossi et al. (2011) experimentally implicated albumin, via p38 mitogen-activated protein kinase, in a novel mechanism by which activation of myosin light chain kinase after TBI may lead to the disruption of the BBB. This finding elucidates how a decrease in albumin levels can result in a poor prognosis for TBI by compromising BBB integrity. Previous studies have demonstrated a strong association between low serum albumin and unfavorable outcomes in TBI patients (Luo et al., 2019). Bernard et al. (2008) reported that serum albumin levels appeared to be an independent predictor of poor outcomes (Glasgow Outcome Scale [GOS]: 1-3) in adult patients with TBI. Serum albumin and prealbumin can also serve as predictors for adult patients with severe TBI (GCS≤8), with serum albumin identified as an independent predictor (D. Chen et al., 2014). Chen et al. (2014) showed that serum albumin levels within 24 hours after admission can predict poor outcomes (GOS: 1-2) in patients with severe TBI. Multiple studies have concluded that serum albumin is a valuable biomarker for both children (Luo et al., 2019) and adult patients (D. Chen et al., 2014) with moderate to severe TBI, particularly in cases where hypoalbuminemia is present. The worsening of hypoalbuminemia is likely to contribute to secondary brain injury and result in increased mortality and morbidity in TBI patients (Luo et al., 2019; Nayak et al., 2020).

## CONCLUSION

TBI continues to be a global health problem throughout the world. Clinical assessment and biomarkers that are appropriate to the pathophysiology of TBI will help to determine the severity and prognosis of patients with TBI. The integrity of the BBB, as assessed by the CFS-blood albumin ratio, may be an option for assessing the severity of TBI. The CSF-blood albumin ratio is associated with biomarkers of neuronal and astroglial injury (NSE and S100b). These two biomarkers have been extensively studied and shown to be associated with the severity, prognosis and outcome of TBI patients. The CSF-blood albumin ratio can be considered as a biomarker to assess the severity of TBI, but further clinical research is needed to confirm this theory.

## AUTHORS' CONTRIBUTION

HIH & PK: Concept and design, data acquisition, interpretation, drafting, final approval, and agree to be accountable for all aspects of the work. BPS, ANU and H: Data acquisition, final approval and agree to be accountable for all aspects of the work.

**Conflict of interest:** Authors declared no conflict of interest.

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