

Review

Recent Advance of S100B Proteins in Spontaneous Intracerebral Hemorrhage and Aneurysmal Subarachnoid Hemorrhage

Zhang-Ming Zhou^{1,†}, Ling-Ling Gu^{2,†}, Zhe-Yu Zhou³, Qing-Le Liang^{4,*}

¹Department of Neurosurgery, Dujiangyan Medical Center, 611800 Chengdu, Sichuan, China

²Department of Anesthesiology, Dujiangyan Medical Center, 611800 Chengdu, Sichuan, China

³Department of Medical Image Science, Shenyang Medical College, 110000 Shenyang, Liaoning, China

⁴Department of Clinical Laboratory Medicine, Chongqing University Jiangjin Hospital, 402260 Chongqing, China

*Correspondence: liangqingle@126.com (Qing-Le Liang)

†These authors contributed equally.

Academic Editor: Thomas Heinbockel

Submitted: 11 July 2023 Revised: 25 September 2023 Accepted: 24 November 2023 Published: 19 January 2024

Abstract

Human health is seriously endangered by spontaneous intracerebral hemorrhage (ICH) and aneurysmal subarachnoid hemorrhage (aSAH). Because the majority of ICH and aSAH survivors experience disability, increased risk of stroke recurrence, cognitive decline, and systemic vascular disease, ICH and aSAH assume special importance in neurological disease. Early detection and prediction of neurological function and understanding of etiology and correction are the basis of successful treatment. ICH and aSAH cause complex inflammatory cascades in the brain. In order to establish precise staging and prognosis, as well as provide a basis for treatment selection and monitoring, it is imperative to determine appropriate biological markers according to pathological and physiological mechanisms. In this review, we focus on the research progress of S100B, an endogenous danger signaling molecule, as a potential biomarker for ICH and aSAH, assisting in the development of further basic research and clinical translational studies.

Keywords: spontaneous intracerebral hemorrhage; aneurysmal subarachnoid hemorrhage; S100B; biomarker; prognosis

1. Introduction

1.1 Epidemiological Characteristics of Spontaneous ICH and aSAH

Spontaneous intracerebral hemorrhage (ICH) refers to the spontaneous rupture of large or small arteries, veins, and capillaries in the brain, causing intracerebral hemorrhage in the brain parenchyma, without traumatic injury. Most commonly, ICH occurs in the basal ganglia. Different bleeding sites manifest different clinical features. According to the etiology, ICH can be divided into primary and secondary. Primary ICH accounts for about 80% to 85% of all cerebral hemorrhages, including hypertensive ICH (which accounts for about 50% to 70%), cerebral amyloid angiopathy (CAA, which accounts for about 20% to 30%), and idiopathic ICH (which accounts for about 10%). Spontaneous ICH accounts for 10% to 15% of all strokes in Western countries, but the proportion is higher in East Asia, ranging from 18.8% to 47.6% [1]. Among all types of strokes, it has the second highest incidence after ischemic stroke. Compared with ischemic stroke (IS), spontaneous ICH has a poorer prognosis, with a high mortality rate and poor functional prognosis, with a 30-day mortality rate of 37%–52%. In the past 20 years, the annual incidence of cerebral hemorrhage in the United States has doubled to about 80,000 cases per year, and it is estimated that 30%–40% of cerebral hemorrhage cases die [2]. A study analyzing 21 countries conducted over the past few decades showed that the total an-

nual incidence of cerebral hemorrhage is 24.6/100,000 per year. The risk estimate increases with age, and in addition, the risk estimate for Asian populations is approximately twice that of Caucasians [3]. In the United States, the risk of cerebral hemorrhage in African Americans and Hispanic populations is about 1.6 times that of Caucasians [4]. The main causes of adult cerebral hemorrhage are hypertension, cerebral amyloid angiopathy, and anticoagulant therapy. Hypertension is the strongest risk factor for cerebral hemorrhage, and subgroup analysis of randomized controlled trials of blood pressure control therapy showed that lowering blood pressure can reduce the incidence of cerebral hemorrhage [5]. Because most cerebral hemorrhage survivors have disabilities and are at risk of stroke recurrence, cognitive decline, and systemic vascular disease, cerebral hemorrhage is of particular importance in neurological diseases. Aneurysmal subarachnoid hemorrhage (aSAH) is widely recognized as a highly fatal manifestation of a severe medical condition, particularly for patients in poor-grade conditions, whose prognoses are notably unpredictable. The main difference between aneurysmal subarachnoid hemorrhage (aSAH) and intracerebral hemorrhage is as follows: In a strict sense, intracerebral hemorrhage refers to bleeding within the brain parenchyma, typically resulting from arteriosclerosis. On the other hand, subarachnoid hemorrhage typically occurs when blood vessels on the surface or at the base of the brain rupture, often associated with



vascular malformations or tumors. Therefore, the brain damage caused by bleeding differs between the two conditions. Intracerebral hemorrhage often leads to localized brain parenchymal injury and secondary brain herniation, which can be life-threatening. In contrast, aSAH involves diffuse blood clots at the base of the brain and the subsequent breakdown of these clots, resulting in brain damage. Hence, these are two distinct diseases that require different clinical management approaches. In the absence of effective interventions, the mortality rate for patients classified as Fisher grade 3 and Hunt-Hess grade III or higher can reach up to 44% [6,7]. Moreover, the prognosis for aSAH patients is further exacerbated in many low- and middle-income countries due to limited access to craniotomy and interventional embolization techniques and facilities. Moreover, aSAH is usually followed by cerebral vasospasm (CVS) or even cerebral infarction in some extreme cases [8,9].

Due to the high mortality rate of spontaneous ICH and aSAH and the disabilities of most survivors, the focus of treatment is to prevent secondary brain damage [10]. Finding specific and highly sensitive predictive indicators and adopting corresponding treatment measures based on the pathological and physiological mechanisms are currently urgent problems that need to be solved domestically and overseas.

The potential usefulness of blood biomarkers in the management of patients with ICH and aSAH lies in their ability to provide valuable diagnostic and prognostic information. Blood biomarkers, such as S100B, have shown promise in predicting hematoma expansion, assessing the severity of brain injury, and predicting patient outcomes. By measuring specific biomarkers, clinicians may be able to triage patients more effectively, guide treatment decisions, and monitor response to therapy. However, further research is needed to validate the utility of blood biomarkers and establish their role in routine clinical practice.

In conclusion, spontaneous ICH and aSAH are serious neurological conditions that require prompt diagnosis and appropriate management. The potential usefulness of blood biomarkers in these conditions offers the possibility of improving patient care by providing valuable diagnostic and prognostic information. Further research in this field may lead to the integration of blood biomarkers into routine clinical practice, ultimately enhancing patient outcomes in ICH and aSAH.

1.2 Pathological Characteristics of Spontaneous ICH and aSAH

The pathological changes of ICH are the mass effect caused by the hematoma at the site of bleeding, leading to ischemia, edema, and toxic damage to nerve cells induced by the degradation products of secondary hematoma. Firstly, the space-occupying effect of the continuously expanding hematoma is one of the mechanisms that induce

brain injury within 4 hours after the onset of ICH. The initial hematoma occupying effect can rupture the surrounding small arteries through sheer force, resulting in secondary bleeding and further expansion of the hematoma [11]. Secondly, the direct toxicity induced by hematoma components and metabolic products, and the inflammation reaction exacerbated the neurologic deficits [12]. Hemolysis leads to the release of hemoglobin, which further breaks down into heme or its oxidized form, causing oxidative stress and aggravating brain edema and neuronal damage [13]. Thirdly, the more important mechanism of the brain cell damage of plasma and red blood cells after ICH is the coagulation cascade, which includes prothrombin and thrombin [14]. After the hematoma is formed, prothrombin and fibrinogen enter the brain and activate the coagulation cascade reaction, and prothrombin is converted into thrombin, which breaks down fibrinogen into fibrin. Although the main function of coagulation cascade reaction is to stop bleeding, thrombin and fibrinogen also have other functions in the brain; for example, thrombin can activate microglia, induce astrocyte proliferation and disrupt the blood-brain barrier, which can lead to brain damage [15].

The primary contributor to craniocerebral injury is axonal white matter injury resulting from aSAH. Brain damage and subsequent pathological changes, particularly the long-term detrimental effects of hemoglobin and inflammatory molecules on the brain, occur approximately one year after patients are admitted to the hospital, which has sparked heightened research interest [16,17]. The fundamental notion of early brain injury (EBI) holds significant importance as it serves as a crucial indicator of the ultimate prognosis [18]. Hence, the Hunt and Hess (H-H) grade, Fisher grade, and the World Federation of Neurological Surgeons (WFNS) scale are frequently employed in prognosticating the outcome of aneurysmal subarachnoid hemorrhage (aSAH). Despite its significance in determining prognosis, the etiology of brain injury in aSAH is complex and not fully comprehended [19].

1.3 Clinical Management of Spontaneous ICH and aSAH

The clinical management of spontaneous ICH involves a multidisciplinary approach, including prompt diagnosis, supportive care, medical management, and surgical interventions. Imaging studies such as computed tomography (CT) scans are crucial for confirming the diagnosis and assessing the size and location of the hematoma. Medical management includes blood pressure control, correction of coagulopathy if present, and management of associated complications such as elevated intracranial pressure and seizures. Surgical interventions, such as hematoma evacuation or decompressive craniectomy, may be considered in selected cases.

On the other hand, aSAH is caused by the rupture of an intracranial aneurysm, leading to bleeding into the subarachnoid space. It is a relatively rare condition but carries

a high risk of mortality and long-term neurological deficits. Risk factors for aSAH include smoking, hypertension, and family history of aneurysms. The classic presentation of aSAH is a sudden, severe headache often described as the worst headache of one's life, accompanied by neck stiffness and neurological deficits.

The management of aSAH involves early diagnosis, securing the aneurysm, and preventing complications. Diagnostic imaging, such as CT scans and angiography, is essential for identifying the site of the aneurysm and determining the extent of bleeding. Endovascular coiling or surgical clipping is performed to secure the aneurysm and prevent rebleeding. Additionally, medical management includes blood pressure control, prevention of vasospasm, and management of complications such as hydrocephalus and seizures. S100B is of interest from a prognostic point of view and in the detection of certain complications (such as delayed cerebral ischemia), but not in the choice of treatment.

1.4 Biomarker S100B

Blood biomarkers are measurable products that reflect the health or pathological processes of the body. An ideal blood biomarker should be simple, fast, and inexpensive. Therefore, BBM should be easily measured and repeatable in accessible tissues, with stability throughout the healthy population. Following a cerebral hemorrhage, blood components are released into brain tissue, first activating intrinsic immune cells such as microglia, and triggering a cascade of inflammatory response signaling pathways that disrupt the blood–brain barrier, leading to peripheral blood immune cell infiltration and activation, and release of various cytokines, chemokines, free radicals, and other toxic substances, forming an immune storm that leads to mass neuron and supporting cell death [20,21]. In addition, 24 hours after ICH occurs, the red blood cells released into the brain tissue are lysed, and the released cytotoxic substances, such as hemoglobin, heme, and iron ions, play an important role in the death of neurons [22]. After neuron death, a series of endogenous damage-associated molecular pattern (DAMP) signals, such as adenosine, heat shock protein (HSP), interleukin-33 (IL-33), and etc., are released and bind to pattern recognition receptors to activate the intrinsic immune response, inducing a malignant cycle of inflammation response–cell death–DAMP release–inflammation response. In recent years, a series of studies focused on the important DAMPs such as heme, high mobility group box 1 (HMGB1), S100B protein (S100B), and peroxiredoxin, which play a vital role in secondary brain injury caused by cerebral hemorrhage (Fig. 1). In this review, we summarize the research progress of S100B in ICH, an endogenous danger signal molecule, to provide reference for further basic research and clinical translational research.

Calcium ions are essential cellular signaling molecules involved in many physiological and pathologi-

cal activities, such as enzyme production, differentiation, proliferation, and even apoptosis [23]. Some proteins can bind to calcium ions in specific areas, exerting multiple functions, known as calcium-binding proteins (CBPs). CBPs are critical components that regulate calcium signal transduction and interaction with different targets, including albumin, calbindin, and calmodulin [24]. They are found in morphologically different interneurons and are involved in a variety of cortical circuits in both normal and abnormal nervous systems; the largest representative of CBPs is the S100 protein family [25].

The S100 protein family, containing over 20 structurally similar CBPs, acts as calcium-activated switches in various tissues and regulates the activity of their target proteins. They represent the largest subgroup of the EF-hand protein superfamily, characterized by a pentameric arrangement of calcium-binding loops around the calcium ion (EF-hand motif). Some members of the S100 protein family bind to zinc and/or copper, indicating the possible involvement of these metals in their biological activity regulation [26]. S100 calcium-binding protein B (S100B) is a protein discovered in the 1960s, named because it can dissolve in a 100% saturated ammonium sulfate solution. S100B is a 21-kDa acidic protein and its gene contains 13 members, which exist in the form of clusters on chromosome 1q21. It consists of two α -helix–loop– α -helix calcium-binding proteins that participate in cell skeleton formation and cell proliferation, forming a homo-dimer. Each subunit contains two EF-hand calcium-binding structures and is connected by a central hinge region [27]. Each subunit also contains four helices (Helix 1, E2–R20; Helix 2, K29–N38; Helix 3, Q50–D61; Helix 4, F70–A83) and one anti-parallel β -fold (Chain 1, K26–K28; Chain 2, E67–D69) that form normal and pseudo-EF hands [28]. S100B has been shown to be concentrated in astrocytes and other neural glial cells, such as oligodendrocytes, Müller cells in the retina, and colonic glial cells. It has also been detected in specific neuronal subpopulations, indicating that S100B is not limited to neural tissue [29]. S100B is a calcium-sensitive protein that regulates various activities within cells, transmits second messenger signals, and interacts with different molecules in different cell types, participating in calcium homeostasis, energy metabolism, cell proliferation, motility, and cytoskeleton regulation [30,31]. S100B is first detected in brain tissue after embryonic day 14 and proportionally increases during neural system development until stabilizing in adulthood [32]. The high value of S100B in newborns is due to mature neuronal activity and glial cells; this phenomenon is also observed in rodents [33]. Changes in S100B during the aging process are related to pro-inflammatory neuropathological events, including ischemia, trauma, and time-related infections [34].

S100B is considered an important biomarker for brain injury, which can be released from damaged or activated cells under cellular stress conditions. S100B protein was

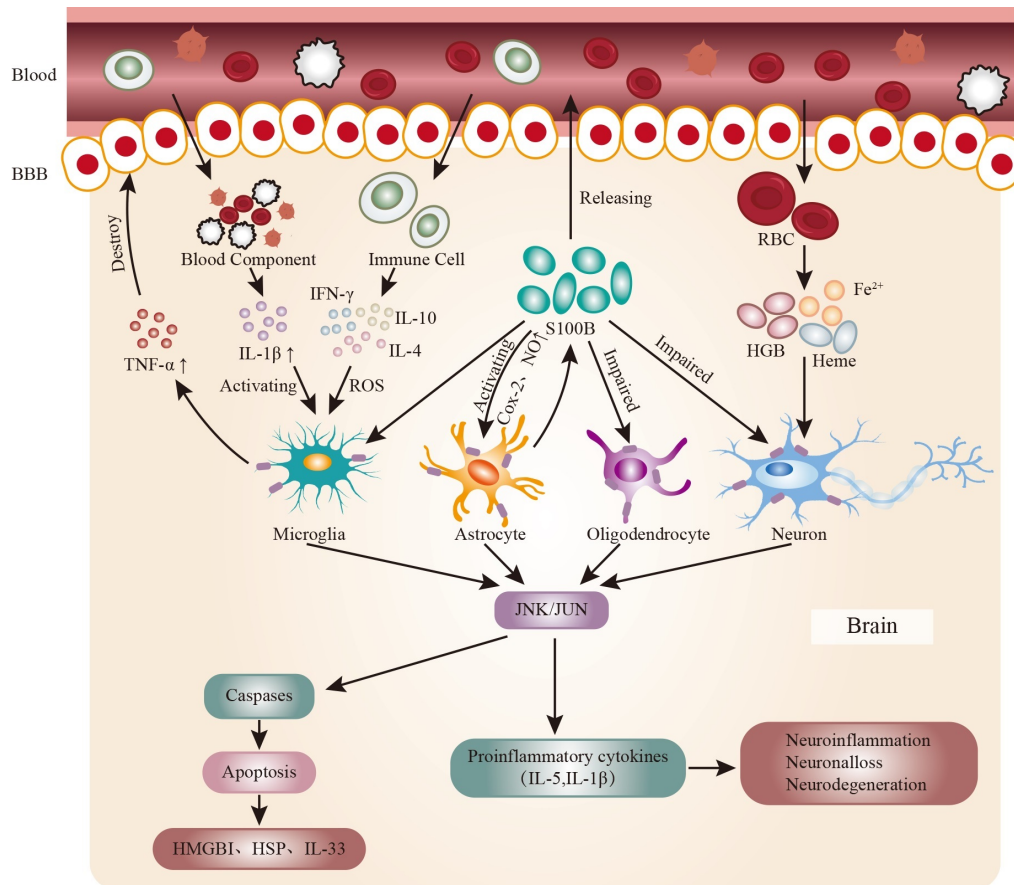


Fig. 1. Pathological features and mechanism of S100B in spontaneous intracerebral hemorrhage. Brain damage is the result of the ongoing inflammatory response occurring in the presence of hematoma products following spontaneous intracerebral hemorrhage. The initial pro-inflammatory phase involves blood components being released into brain tissue, activating microglia, and triggering a cascade of inflammatory response signaling pathways that disrupt the blood–brain barrier (BBB), leading to peripheral blood immune cell infiltration and activation, and release of various cytokines, chemokines, free radicals, and other toxic substances, forming an immune storm that leads to mass neuron and supporting cell apoptosis. S100B is released from damaged cells under cellular stress conditions, leading to the overactivation of S100B protein which increases proinflammatory markers release and neurodegeneration. BBB, blood–brain barrier; RBC, red blood cell; HGB, Hemoglobin; IFN- γ , interferon- γ ; TNF- α , tumor necrosis factor- α ; ROS, reactive oxygen species; HMGB1, high mobility group box 1; HSP, heat shock protein.

first detected in the cerebrospinal fluid (CSF) of patients with multiple sclerosis (MS). In the acute phase, levels of this protein are elevated, while in the quiescent phase, they are lower. It is difficult to perform pathological biopsies for neurological diseases, the expression levels of S100B in cerebrospinal fluid or peripheral blood have gradually been viewed as important biomarkers for neurological damage. Currently, S100B has been found to increase in conditions such as acute brain injury, neurodegenerative diseases, MS, congenital/perinatal disorders, and psychiatric disorders [35]. In instances of central nervous system damage, S100B protein is released from damaged brain cells, and enters the bloodstream through the blood–brain barrier. Its expression level is closely related to the degree of injury and prognosis [36]. S100B can also be detected in body fluids such as umbilical cord blood [37], amniotic fluid [38], urine [39], and saliva [40]. In mammals,

S100B protein is metabolized and excreted by the kidneys, and has a half-life of 2 hours. S100B protein is predominantly found in the brain, with a high concentration (3500 ng/mg protein) in the central nervous system, comprising 0.1% to 0.2% of the total soluble protein [41]. S100B protein has a dose-dependent dual function. In physiological levels, i.e., picomolar or nanomolar levels, S100B protein has a neurotrophic effect. In micromolar levels, S100B protein has a neurotoxic effect, inducing the release of pro-inflammatory cytokines, such as interleukin-1 β (IL-1 β), tumor necrosis factor- α (TNF- α), and inducible nitric oxide synthase (iNOS), inducing neuron death through nitric oxide-dependent pathways. Overexpression of S100B protein can induce neurodegenerative lesions via calcium-dependent pathways [42]. A high level of S100B was relevant with a poor prognosis. Therefore, S100B is considered an important biomarker for brain injury [43,44].

2. S100B and Cerebral Hemorrhage

2.1 Spontaneous Intracerebral Hemorrhage

The poor prognosis of spontaneous cerebral hemorrhage is higher than that of cerebral infarction. Hemorrhagic injury after spontaneous cerebral hemorrhage involves complex inflammatory cascades. S100B stimulates the release of inflammatory factors such as IL-1, IL-6, and TNF- α , and is associated with disease progression. S100B levels in cerebrospinal fluid and blood are currently considered reliable biomarkers of acute brain injury caused by cardiovascular disease or traumatic injury and are also considered predictive indicators of prognosis for these patients [45]. Empirical evidence has demonstrated the pivotal role of S100B in the inflammatory processes following ICH. This multifunctional protein facilitates the activation of microglia and astrocytes, instigating the release of pro-inflammatory cytokines and chemokines. Moreover, S100B engages with receptors on endothelial cells, fostering blood–brain barrier disruption and the formation of edema. By selectively targeting S100B and its downstream signaling cascades, researchers aspire to forge innovative therapeutic strategies capable of modulating the inflammatory response and curtailing cerebral injury in the context of ICH. In a rat model of cerebral hemorrhage constructed by type IV collagenase, serum S100B levels reached a peak six hours after hemorrhage [46]. It was found that the severity, mortality, and functional prognosis of ICH patients were related to the level of S100B protein in peripheral blood, the dynamic changes in S100B are closely related to mortality rates. The serum S100B levels on admission, the first day of admission, and the second day of admission of patients with ICH can distinguish between survivors and non-survivors six months after onset. In addition, it has been found that there is a correlation between S100B levels and clinical tomographic results, severity scores, and outcome scale scores [47]. Delgado *et al.* [48] found that higher S100B levels in serum within 24 hours are associated with larger hematoma volume, early neurological deterioration, and poor functional prognosis. Hu *et al.* [49] found a correlation between S100B serum levels in patients with ICH and hematoma volume, Glasgow Coma Scale (GCS) score, and mortality rate. Alatas *et al.* [50] found that the peripheral blood S100B protein levels of patients with ICH increased significantly on the 0th and 5th day compared with the normal control group and were negatively correlated with the GCS score while positively correlated with the National Institutes of Health Stroke Scale score and bleeding volume. The serum S100B levels of deceased patients increased significantly, indicating that higher serum S100B levels are associated with larger hematoma volumes and mortality rates. Kumar *et al.* [51] confirmed that S100B protein can improve the accuracy of short-term and long-term prognosis judgments after ICH. Studies have shown that the serum S100B levels of patients with cerebral hemorrhage are significantly higher than those of patients with

ischemic stroke, which can be used to differentiate between the two types of strokes [52]. Ferrete-Araujo *et al.* [47] conducted a prospective study of 36 patients with cerebral hemorrhage and found that the serum S100B levels of deceased patients were higher on admission, 24 hours, and 48 hours after onset than those of surviving patients. Among surviving patients, the serum S100B levels of patients with poor prognosis were higher than those with a good prognosis after 24, 48, and 72 hours after onset. This implies that serum S100B is an early predictive marker of poor neurological prognosis and mortality in patients with cerebral hemorrhage. Therefore, S100B, as a biological indicator, has certain clinical significance for the diagnosis and prognosis of ICH, and can help clinicians stratify patients and make early referrals and interventions.

A pivotal development in this area is the emergence of highly sensitive and specific assays capable of precisely measuring S100B concentrations in blood samples [43]. These assays enable rapid and accurate quantification of S100B, thereby facilitating its utilization as a diagnostic and prognostic tool in ICH. Studies have consistently demonstrated that elevated S100B levels in the bloodstream are closely associated with larger hematoma volumes, heightened risk of hematoma expansion, and unfavorable clinical outcomes in patients afflicted by ICH. Armed with this invaluable information, clinicians can make more informed decisions pertaining to the management and treatment strategies employed for individuals suffering from ICH. In addition to its diagnostic and prognostic significance, recent investigations have provided insight into the underlying pathophysiological mechanisms driving the inflammatory cascade following intracerebral hemorrhage (ICH). It is widely recognized that ICH elicits a series of inflammatory responses within the brain, culminating in secondary brain injury and neurological deterioration. Elucidating these intricate pathways is pivotal for devising targeted therapeutic interventions aimed at mitigating the inflammatory response and enhancing patient outcomes.

However, several important factors need to be taken into account when considering the measurement of plasma S100B levels in patients with ICH, including the optimal timing of measurement, frequency of measurements, the impact of intra-individual variability, and the non-interchangeability of decision thresholds. To date, consensus has not been reached regarding the ideal time of measurement for plasma S100B levels in patients with ICH. Previous studies have demonstrated a rapid increase in plasma S100B levels within 6 hours following ICH, reaching a peak at 24 hours, remaining stable on the second day, and gradually decreasing thereafter. However, conflicting findings have emerged from other studies, reporting different patterns of S100B release and clearance. Consequently, further investigation is necessary to establish the most appropriate time points for measurement, ensuring the acquisition of accurate and clinically relevant information.

Intra-individual variability refers to the natural fluctuations in S100B levels within an individual over a period of time. This variability can impact the interpretation and clinical significance of S100B values. It is important to consider this variability when using S100B as a biomarker for ICH. Longitudinal studies that include multiple measurements within the same individuals can help determine the extent of intra-individual variability and its impact on the interpretation of S100B levels.

The frequency of measurements is also a crucial consideration when assessing plasma S100B levels in patients with ICH. The aforementioned study conducted measurements on days 1, 2, 3, 5, and 7 post-ICH to investigate temporal changes in S100B levels. Nonetheless, the optimal frequency of measurements may vary depending on the specific research question and clinical context. For instance, more frequent measurements may be required during the acute phase to monitor dynamic changes in S100B levels, whereas fewer measurements may suffice for prognostic purposes.

S100B has garnered significant attention in the field of neurology due to its potential as a prognostic biomarker and its role in detecting complications, specifically delayed cerebral ischemia (DCI), in various neurological conditions.

In terms of prognosis, elevated levels of S100B in the bloodstream have been consistently associated with worse outcomes in conditions such as traumatic brain injury, intracerebral hemorrhage (ICH), and aneurysmal subarachnoid hemorrhage (aSAH). In the context of ICH and aSAH, higher levels of S100B have been correlated with larger hematoma volumes, an increased risk of hematoma expansion, and poorer clinical outcomes. Numerous studies have demonstrated that S100B levels can effectively predict long-term functional outcomes, as assessed by the Glasgow Outcome Scale (GOS), a widely used tool to evaluate neurological recovery and disability. Higher S100B levels are frequently associated with a reduced likelihood of achieving a favorable GOS score, indicating a poorer prognosis.

In addition to its prognostic value, S100B has shown promise in the early detection of complications, particularly DCI, in patients with aSAH. DCI refers to the delayed onset of cerebral ischemia that occurs several days after the initial hemorrhage and is associated with significant morbidity and mortality. Research has indicated that elevated S100B levels can serve as an early marker for the development of DCI. Regular monitoring of S100B levels in these patients provides clinicians with the opportunity to initiate preventive measures or promptly adjust management strategies (Table 1, Ref. [35,44,49,52–59]).

Overall, the quantification of S100B as a circulating biomarker holds immense potential in predicting outcomes and detecting complications in neurological conditions such as ICH and aSAH. Continued research and validation of S100B's utility in these contexts will further enhance its

clinical applicability and improve patient care. In summary, recent advances in understanding the role of S100B proteins in spontaneous intracerebral hemorrhages and aneurysmal subarachnoid hemorrhages have shed light on their potential as prognostic biomarkers and their ability to detect complications. Elevated levels of S100B have been associated with worse outcomes and can predict long-term functional recovery in these conditions. Additionally, S100B can serve as an early marker for complications such as delayed cerebral ischemia. However, it is important to note that S100B should be interpreted in conjunction with other clinical and radiological parameters and should not be the sole determinant for treatment decisions. Further research is needed to fully establish the clinical utility of S100B and its integration into routine practice.

2.1.1 Prognostic Utility

Several studies have investigated the prognostic value of S100B protein levels in patients with spontaneous intracerebral hemorrhage (ICH) and aneurysmal subarachnoid hemorrhage (aSAH). In a study by Foerch *et al.* [60], it was found that higher S100B levels at admission were associated with larger hematoma volumes and poorer clinical outcomes in patients with ICH. Similarly, a study by Kedziora *et al.* [58] demonstrated that elevated S100B levels were predictive of worse functional outcomes at 6 months post-aSAH. These findings suggest that measuring S100B protein levels at admission could serve as a useful prognostic tool in these conditions.

2.1.2 Detection of Complications

The detection of complications, particularly delayed cerebral ischemia (DCI), is crucial in the management of patients with aSAH. Several studies have examined the utility of measuring S100B protein levels in predicting the development of DCI. In a study by Kedziora *et al.* [58], elevated S100B levels within 48 hours of aSAH were found to be associated with a significantly higher risk of subsequent DCI. Another study by Azurmendi *et al.* [61] demonstrated that S100B levels measured within 72 hours of aSAH were able to predict the occurrence of DCI with high sensitivity and specificity. These findings suggest that early measurement of S100B protein levels can serve as an important tool in identifying patients at risk of developing DCI.

It is important to note that while these studies provide valuable insights into the potential utility of measuring S100B protein levels in prognostication and the detection of complications, further research is still needed. There is a need for larger, well-designed prospective studies to establish the precise thresholds and clinical implications of S100B protein measurements in these contexts. Additionally, the integration of S100B protein measurements into routine clinical practice should be carefully considered in conjunction with other clinical and radiological parameters.

Table 1. Studies on S100B Proteins in Spontaneous Intracerebral Hemorrhage (ICHs) and Aneurysmal Subarachnoid Hemorrhages (aSAHs).

Author (year)	Reference	Sample size	Prognostic score	Measurement technique	Decision threshold	Diagnostic performance
Herrmann <i>et al.</i> (2000) [53]	PMID: 10709869	50	GOS at 6 months	ELISA	>0.25 µg/L	Sensitivity: 64%, Specificity: 86%
Hu <i>et al.</i> (2010) [49]	PMID: 21778425	86	1-week mortality of patients	ELISA	>192.5 pg/mL	Sensitivity: 93.8%, Specificity: 70.4%
Petzold <i>et al.</i> (2002) [44]	PMID: 12483062	20	The mortality of the patients	In-house ELISA	60 pg/mL within the first 24 hours (serum)	Sensitivity: 100%, Specificity: 75%
Oertel <i>et al.</i> (2006) [54]	PMID: 16720181	51	Vasospasm, GOS at 6 months	ELISA	>1 µg/L	Sensitivity: 95.8%, Specificity: 84.6%
Sanchez-Peña <i>et al.</i> (2008) [55]	PMID: 18679180	163	GOS at 12 months	ELISA	>0.23 µg/L	Sensitivity: 91%, Specificity: 90%
Stranjalis <i>et al.</i> (2007) [35]	PMID: 17242846	52	GOS at 1 year	ELISA	>0.3 µg/L	Sensitivity: 76%, Specificity: 77.8%
Zhou <i>et al.</i> (2016) [52]	PMID: 27078704	46	NIHSS and mRS	ELISA	>67 pg/mL	Sensitivity: 95.7%, Specificity: 70.4%
Balança <i>et al.</i> (2020) [56]	PMID: 32545872	81	M-GCS at admission, M-GCS at day 3	ELISA	>0.165 µg/L	AUC: 84.1% (M-GCS at admission), 88.2% (M-GCS at day 3)
Kedziora <i>et al.</i> (2020) [57]	PMID: 33333873	60	In-hospital mortality	ELISA	>1.8 ng/mL (blood), >80.0 ng/mL (CSF)	AUC: 0.873 (blood), 0.889 (CSF)
Kedziora <i>et al.</i> (2021) [58]	PMID: 33291504	55	ICU outcome based on GOS	ELISA	>0.625 ng/mL	Sensitivity: 91.3% Specificity: 62.5%
Uryga <i>et al.</i> (2021) [59]	PMID: 33610360	55	GOS at discharge, mRS at long-term follow-up	ELISA	>1.90 ng/mL	Sensitivity: 75%, Specificity: 81%

ELISA, Enzyme Linked Immunosorbent Assay; NIHSS, National Institute of Health Stroke Scale; M-GCS, Motor component of the Glasgow coma scale; CSF, Cerebrospinal Fluid; ICU, Intensive Care Unit; GOS, Glasgow Outcome Scale.

In conclusion, studies have shown that measuring S100B protein levels can provide valuable prognostic information in patients with spontaneous ICH and aSAH. Elevated levels of S100B at admission have been associated with larger hematoma volumes and worse clinical outcomes. Furthermore, S100B protein levels have shown promise in the early detection of complications, particularly DCI, in patients with aSAH. However, further research is needed to establish precise thresholds and clinical implications, as well as to determine the optimal integration of S100B protein measurements into routine clinical practice.

Regarding the potential use of biomarkers in this context, the most recent guidelines (American Heart Association/American Stroke Association) [62] concerning the management of aSAH patients identified knowledge gaps concerning the use of blood biomarkers and stated the need for future research on improving biomarkers for injury and outcome prediction.

In summary, S100B protein levels are primarily used for prognostication and the detection of complications in various neurological conditions. While elevated levels of S100B may indicate worse outcomes and predict the occurrence of complications, it is not used as a sole determinant for differentiating between specific types of brain injury, such as cerebral hemorrhage and ischemic damage.

2.2 Aneurysmal Subarachnoid Hemorrhage

Aneurysmal subarachnoid hemorrhage (aSAH) accounts for only 5% of all stroke events, but it has a death rate of approximately 50% (32%–67%) and affects a relatively young age group compared to ischemic stroke [52]. The pathophysiology of early brain injury and secondary brain injury after aSAH is not fully understood, but abundant evidence supports the key role of inflammation in aSAH. Accurate prognosis in the early stages of the disease is very difficult, but Kellerman *et al.* [45] reported that S100B values >0.7 $\mu\text{g/L}$ after aSAH are associated with a 100% mortality rate, and they suggest that S100B levels may be used to guide clinical decisions. Quintard *et al.* [63] found that elevated peripheral blood S100B levels in the first week after aSAH are associated with poor neurological prognosis, with the predictive value of S100B levels being strongest on the fifth day. However, Heikki *et al.* [64] tested S100B levels of 47 aSAH patients for up to 5 days and concluded that S100B levels are not related to neurologic prognosis 6 months after aSAH. Elevated S100B levels on the first day after aSAH are closely related to mild initial clinical manifestations. Recently, we found that neurofilament light chain (NfL) and S100B serum levels are associated with disease severity and outcome in patients with aneurysmal subarachnoid hemorrhage (aSAH), serum NfL and S100B levels are linked to poor prognoses and low survival rates. The blood levels of NfL and S100B were found to be an independent predictor related to 6-month mortality in multivariable analysis [65]. Oertel *et al.* [54] conducted a study

investigating the relationship between S100B and neuronal-specific enolase (NSE) in aSAH patients. The findings suggested that elevated levels of both S100B and NSE are associated with the severity of initial brain injury and can be used to predict the development of vasospasm. This indicates that S100B and NSE can serve as complementary biomarkers for assessing the initial impact of aSAH and predicting the risk of vasospasm. Sanchez-Peña *et al.* [55] examined the prognostic value of S100B in aSAH patients. Their study revealed that higher levels of S100B are correlated with poor clinical outcomes, including disability and mortality. This highlights S100B as an additional prognostic marker, providing valuable information for predicting outcomes in aSAH patients.

Furthermore, Balança *et al.* [56] and Kedziora *et al.* [57,58] conducted studies on the diagnostic accuracy and predictive value of S100B in aSAH. They found that early measurement of S100B serum concentration can be a useful diagnostic marker for aSAH and has the potential to predict neurological outcomes. These results indicate that S100B may aid in the early identification of aSAH and serve as a prognostic indicator for clinical outcomes.

Moreover, the wash-out pattern of S100B in the CSF has been found to demonstrate a rapid decline over time. This suggests that S100B can be used as an early marker for assessing the severity of the initial brain injury in aSAH patients. The rapid decrease in S100B levels can indicate the resolution of the acute insult and potentially provide valuable information for treatment decisions and prognostication.

However, it is important to note that there are limitations to the use of S100B as a biomarker in aSAH. One limitation is the lack of standardized protocols for measuring S100B levels. There can be variability in the assays used for S100B measurement, which can affect the accuracy and comparability of results across studies. Additionally, the timing of sample collection and the specific cutoff values used for defining elevated S100B levels may vary among studies, making it challenging to establish consistent diagnostic and prognostic thresholds.

Another limitation is the potential influence of extracranial sources on S100B levels. S100B is not specific to brain tissue and can be released from other tissues, such as skeletal muscle and adipose tissue, in response to injury. This can lead to false-positive results or confound the interpretation of S100B levels in aSAH patients. Therefore, it is crucial to consider and account for potential extracranial sources of S100B when interpreting its levels in aSAH patients.

In addition to S100B, other biomarkers and pathophysiological mechanisms have been explored in the context of aSAH. Balança *et al.* [66] provided an overview of damage-associated molecular patterns (DAMPs) and the receptor for advanced glycation end products (RAGE) in the acute phase of brain injury. Their study discussed the

potential involvement of these biomarkers and mechanisms in the pathophysiology of aSAH. Uryga *et al.* [59] investigated the role of serum biomarkers and cerebral autoregulation in predicting the risk of delayed cerebral ischemia in aSAH patients. These studies highlight the broader research efforts to identify and understand various biomarkers and pathophysiological mechanisms associated with aSAH.

It is important to note that while these medical parameters have shown associations with clinical outcomes in aSAH, their precise prognostic value and impact on treatment outcomes require additional research. Future studies should focus on large-scale prospective trials to validate these associations and assess their potential utility in guiding management decisions for aSAH patients.

Overall, the studies mentioned above contribute to the growing body of evidence supporting the potential of S100B as a biomarker for assessing the initial impact of aSAH, predicting clinical outcomes, and complementing other biomarkers in this field. However, further research is still needed to establish standardized protocols, define optimal cutoff values, and explore the utility of combining multiple biomarkers for a more comprehensive assessment of aSAH patients. Therefore, the prognostic judgment of S100B on aSAH is still controversial, and the use of S100B level to guide clinical decision making still needs to be further explored.

3. Summary and Perspectives

In clinical settings, S100B protein, as a biomarker, plays an important role in the diagnosis, differential diagnosis, and prognosis of cerebrovascular diseases. In laboratory research, the S100B protein also acts as a cytokine, participating in the pathophysiological processes of cerebrovascular diseases. Therefore, by reflecting the degree of neuronal damage indirectly through the concentration of S100B in serum or cerebrospinal fluid, it is possible to quantitatively analyze injuries that are difficult to quantify by imaging; simultaneously, by evaluating the therapeutic effects of treatments such as thrombolysis, mechanical thrombectomy, and carotid artery stenting through the dynamic changes in S100B levels, it is possible to monitor the severity of reperfusion injury. Furthermore, there is a possibility that S100B can be used to screen brain cell protective drugs, as well as evaluate the prognosis, and also support the effectiveness of treatment plans. Due to the multiple biological activities of S100B, further research is needed to explore the detection methods in samples, the standard values in serum, the time of blood collection after surgery, the peak time of concentration elevation, and the time to recover to normal levels. Larger sample sizes and more accurately designed studies are needed to provide a basis for clinical treatment plans.

Taken collectively, the recent advancements in S100B measurement as a blood biomarker, coupled with an enhanced understanding of the pathophysiological pathways

driving post-ICH inflammation, have opened up novel avenues for the clinical management of this debilitating condition. Further investigation and clinical trials are imperative to corroborate the utility of S100B as a biomarker and explore its potential as a therapeutic target in the area of ICH.

Author Contributions

ZMZ, LLG, ZYZ and QLL designed, wrote and revised the manuscript, and ZMZ was a major contributor in writing the manuscript and prepared the figure. LLG and ZYZ also participated in the analysing data of the manuscript. LLG and ZYZ made significant revisions and proofread the manuscript. All authors contributed to the article and approved the final version. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

We thank Qian Zhang for modifying figures in the article.

Funding

This work was supported by Chinese public hospital high-quality development of scientific research project fund (No. JL-C016).

Conflict of Interest

The authors declare no conflict of interest.

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