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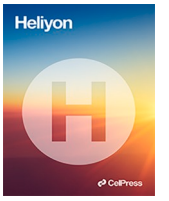

Review article

Acute albumin administration as therapy for intracerebral hemorrhage: A literature review

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ABSTRACT

Intracerebral hemorrhage (ICH) is a subtype of stroke with high mortality. Secondary brain injury after surviving the initial ictus leads to severe neurological deficits, and has emerged as an attractive therapeutic target. Human serum albumin (HSA), a pluripotent protein synthesized mainly in the liver, has shown remarkable efficacy by targeting secondary brain injury pathways in rodent models of ICH, while results from relevant clinical research on albumin therapy remain unclear. Preclinical studies have shown albumin-mediated neuroprotection may stem from its biological functions, including its major antioxidation activity, anti-inflammatory responses, and anti-apoptosis. HSA treatment provides neuroprotective and recovery enhancement effects via improving short and long-term neurologic function, maintaining blood-brain barrier (BBB) integrity and reducing neuronal oxidative stress and apoptosis. Retrospective clinical studies have shown that admission hypoalbuminemia is a prognostic factor for poor outcomes in patients with ICH. However, clinical trial was terminated due to poor enrollment and its potential adverse effects. This review provides an overview of the physiological properties of albumin, as well as its potential neuroprotective and prognostic value and the resulting clinical implications.

1. Introduction

Intracerebral hemorrhage (ICH) constitutes about 10–15 % of all strokes and is associated with high mortality and morbidity [1]. Unfortunately, no surgical treatment is clearly beneficial (except the unpublished ENRICH study). Acute blood pressure lowering and reversal of warfarin-related coagulopathy can be effective [2]. For patients surviving the initial ictus, they are very likely to suffer from severe neurological deficits and death caused by secondary brain injury. In individuals with ICH, secondary brain injury—which includes perihematomal tissue damage from hematoma expansion, inflammatory cascade activation, and release of hematoma breakdown products—is a possible therapeutic target [3,4]. Albumin has been identified as a potentially protective agent in cerebrovascular and cardiovascular diseases, mainly owing to its regulation on the hemodynamics of the brain circulation, anti-oxidant and anti-inflammatory properties. A large number of preclinical studies have unveiled human serum albumin (HSA) is a favorable neuroprotective agent when used at appropriate doses in focal cerebral ischemia, global cerebral ischemia [5,6], subarachnoid hemorrhage [7], and traumatic brain injury [8],while there is no trial in humans showing benefit.

Herein, we reviewed preclinical and clinical findings of albumin. The purpose of this review is to provide an overview of the physiological functions of albumin, as well as its potential neuroprotective and prognostic value and the resulting clinical implications.

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2. Methods

2.1. Search Strategy

This review was conducted by searching the PubMed, Web of Science and ClinicalTrials.gov from inception to March 24th, 2023 for studies focusing on ICH and Albumin. We included preclinical, prospective, retrospective or cohort-based studies. For each search, the keyword combinations were ('ICH' OR 'Intracerebral hemorrhage 'OR 'Intracranial hemorrhage') AND ('Albumin') (Fig. 1).

3. Secondary injury after ICH and possible therapeutic targets

Secondary injury following ICH, which increases mortality and long-term functional disability, has become a promising therapeutic target [1,3,4]. Cell death and the development of cytotoxic edema occur shortly after the ICH due to the mass effect of hematoma [9]. Thrombin activates coagulation cascade and pronounced inflammatory responses, including leukocyte chemotaxis, cytokine release, promotion of blood-brain barrier (BBB) breakdown, etc. [10] BBB breakdown activates the complement cascade in the perihematomal parenchyma and further intensifies inflammatory responses [11]. The hematoma begins to shrink between 72 h and 14 days after the onset of ICH. This is accompanied by erythrocyte lysis and erythrophagocytosis. Accordingly the release of free ions and unconjugated bilirubin can result in secondary injury, which will inhibit NA^{+}/K^{+} adenosine triphosphatase activity, produce hydroxyl radicals, stimulate lipid peroxidation, and result in neural death [12,13]. Oxidative stress is a major cause of secondary brain injury in ICH, which harms central nervous system through impacting inflammation, inducing cell apoptosis and exacerbating damage of BBB [14]. The impetus to investigate the beneficial effects of albumin in ICH derives from their potential interactions overlapping with some of the pathways of ICH-induced secondary brain injury.

4. Potential mechanisms of albumin

Human albumin is a small globular protein (67 kDa) comprised of 609 amino acids. In healthy humans, the liver primarily produces

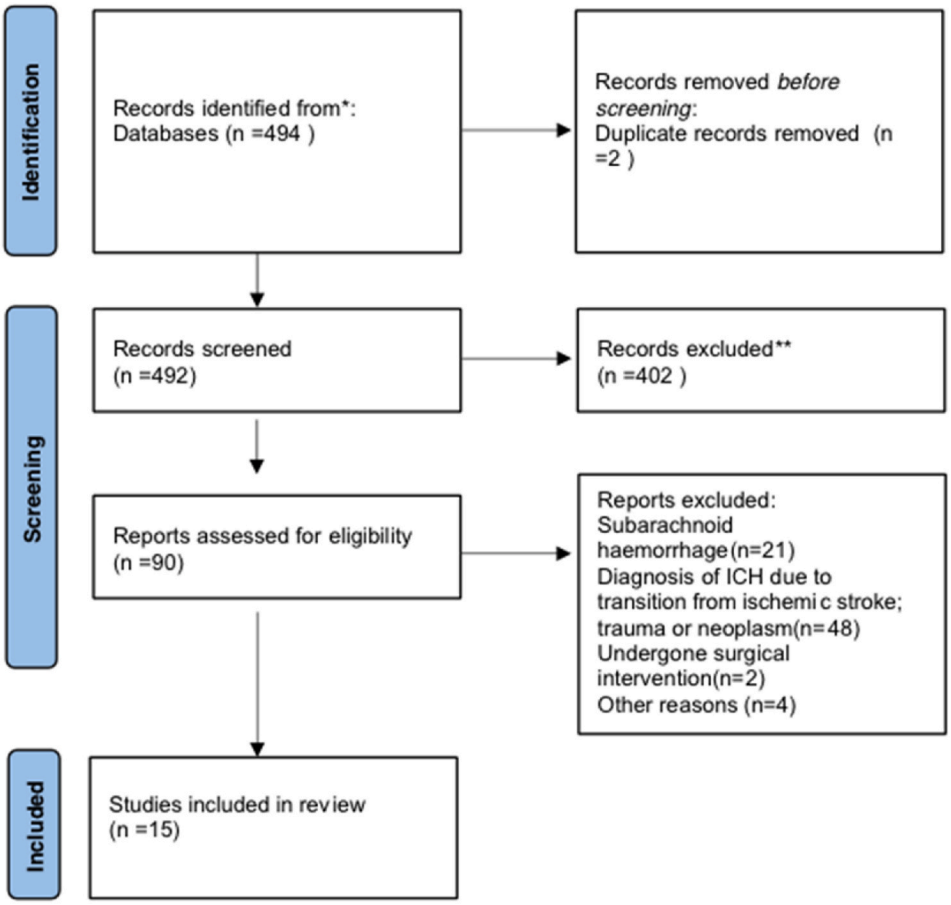

Fig. 1. PRISMA flow diagram outlining the study selection process. PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses.

it at a rate of 9–14 g/day, with a half-life of 12–20 days. It comprises a free cysteine residue (Cys-34) that is the precursor of the molecule's simply free redox-active thiol (-SH) moiety, which may undergo thiolation, nitrosylation, and oxidation [15]. The vast majority of produced albumin enters the extracellular space of muscle and skin, and only about a third remaining in plasma. Most organs catabolize albumin by absorbing it into endocytotic vesicles on the surface of the endothelial cells [16]. Although albumin is primarily a blood-derived protein and enters the cerebrospinal fluid (CSF) through the leptomeningeal blood-CSF barrier (BCSFB) or the choroid plexus BCSFB [17], the precise role of CSF albumin is unknown yet. Ahn, Sung-Min and his colleagues found evidence that microglial cells in the brain may synthesize albumin and play a beneficial role through inhibiting Aβ polymerization and increasing its clearance in Alzheimer's disease (AD) [18].

Albumin is a pleiotropic protein with multiple properties, such as the maintenance of colloid osmotic pressure of plasma (COP); transportation of substances; microvascular permeability regulation; anti-oxidation activity; anti-inflammatory activity; anti-apoptosis and anti-coagulation [19]. Of relevance is that it can target many mechanisms of secondary brain injury, which offers a compelling justification for assuming that albumin therapy would be favorable for ICH patients. Herein, we only review the physiological properties related to neuroprotection and its relevance to ICH(Fig. 2).

4.1. Maintenance of COP of plasma

Albumin accounts for more than half of plasma protein molecules in healthy individuals. Its net negative charge facilitates the attraction of surrounding molecules of sodium, thus holding water. Albumin is responsible for 75–80 % of COP in the basal physiological state [15,19]. As a result of the hypoalbuminemia, the COP is off balance, allowing fluid to extravasate into the interstitial space and cause fluid edema, hypovolemia, and edema of the pulmonary system. In experimental cerebral ischemia, HSA treatment reduces brain edema and normalizes brain water homeostasis [6].

4.2. Transport

Through the usage of electrostatic force and binding sites produced within its tertiary structure, albumin has the capacity to transport and store a wide range of endogenous and exogenous substances, which provides the basis of its potent anti-oxidation activity.

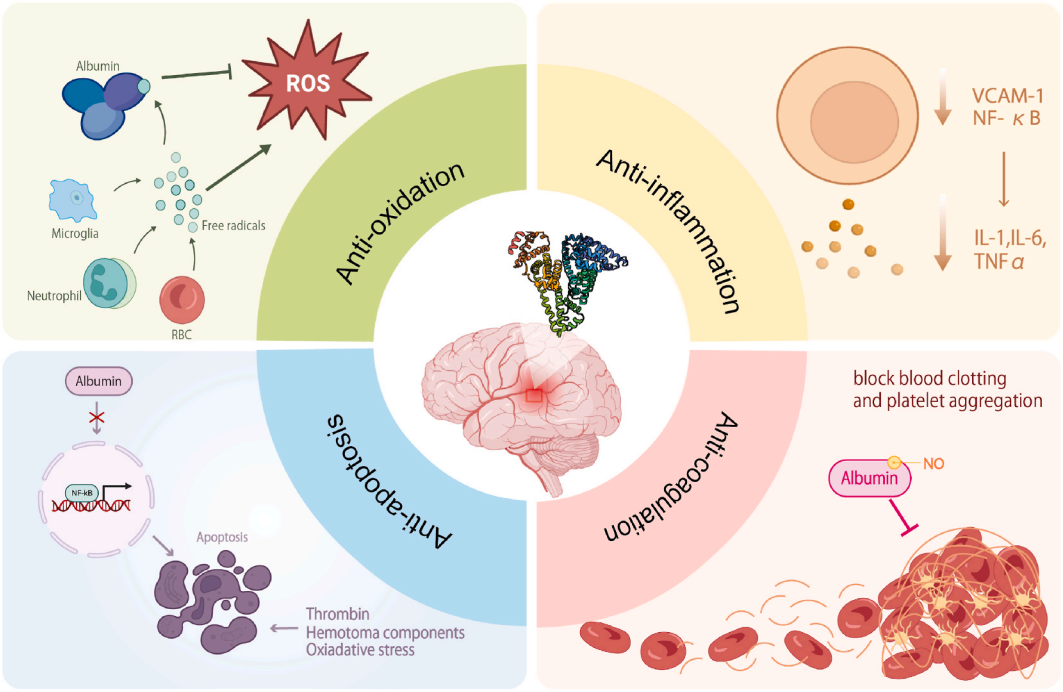

Fig. 2. Potential mechanisms of albumin in ICH preclinical model.(Upper left) Albumin can bind to free radicals and function as a potent anti-oxidant. (Upper right) Albumin can down regulate pro-inflammatory cytokines and VCAM-1 and NF- κB pathways. (Lower left) Albumin can exert anti-apoptosis property via inhibiting NF- κB pathway. (Lower right) Albumin can block blood blotting and platelet aggregation which depends on its ability to bind NO. RBC, red blood cell, VCAM-1,TNF-α, tumor necrosis factor-α, VCAM-1, vascular cell adhesion molecule-1, NF- κB, nuclear factor κB, NO, nitric oxide.

4.3. Anti-oxidation

The most significant scavenger of reactive oxygen species (ROS), the thiol group of Cys34, mediates the anti-oxidation properties of albumin. Cys34 combines with free cysteine or glutathione to form a disulfide under conditions of oxidative stress brought on by ROS. The distinct properties of albumin isoforms, including mercaptalbumin (reduced albumin, HMA) and non-mercaptalbumin-1 and -2 (oxidized albumin, HNA-1 and HNA-2), is assured by the redox status of the thiol group of the Cys34 residue. The excessive generation of free radicals, which causes additional neuronal damage and death, is a central oxidative stress event in ICH. Free radicals are produced by two main pathways: first, by the byproducts of blood cell breakdown such as iron ions, heme, and thrombin; second, by inflammatory cells, such as neutrophils and microglias [20]. Albumin functions as a powerful heme-binding protein. Heme is thought to have pro-oxidant characteristics through facilitating the production of ROS [21].Albumin also binds to irons and other metals,

Table 1
Preclinical findings of albumin treatment.

Reference	Animal ICH model	Groups	Time to treatment after ICH induction	Treatment duration	Neurologic outcomes	Other outcomes
[37]	Sprague-Dawley rats; double-injection method: 100 μL of heparinized fresh autologous blood; left striatum	ICH + vehicle (0.9 %),n = 6 ICH + albumin (1.25 g/kg), n = 8	1.5h	7d	Progressively improved neurobehavior score at 48h to 7 d No influence on histological or MRI lesion size	/
[38]	Sprague-Dawley rats; single-injection method: 50 μL of fresh autologous blood; medicerebral cortex	ICH + vehicle (0.9 %),n = 15 ICH + albumin (1.25 g/kg), n = 14	1h	7d	Improved neurobehavior score within 1–2h,highly significant by 4h Better recovery at each time point Identical total hematoma volume; 38 %–43 % lower mean total neuro scores	No significant differences in physiological variables (Rectal and cranial (temporalis muscle) temperatures, arterial blood pressure and blood gases, and plasma glucose levels) between group; markedly reduced by 49 % Evans blue extravasation, suggesting improved BBB integrity; Not affected brain swelling
[39]	Sprague-Dawley rats; double-injection method 100 μL of fresh autologous blood; right striatum	Sham, n = 12 ICH + vehicle, n = 12 ICH + albumin (0.625 g/kg), n = 12 ICH + albumin (1.25 g/kg), n = 12 ICH + albumin (2.5 g/kg), n = 12	1 h	28d	Improved short-term neurological deficits at 24h and 72h (modified Garcia test, left forelimb placement test, and corner turn test); Improved long-term neurological deficits on 28d (rotarod test, water maze testing)	Increased endogenous albumin and HO-1 expression; reduced neuronal apoptosis (FJC staining and TUNEL staining), neuronal degeneration, ipsilateral hemisphere OS damage (MDA, SOD and 8-OHdG measurements) at 72h via ERK/Nrf2/HO-1 signaling pathway
[40]	Sprague-Dawley rats; double-injection method 100 μL of fresh autologous blood; right striatum	Sham, n = 6 ICH, n = 6	/	/	/	Albumin is the 5th most secreted proteins in brain tissue post-ICH. Bioinformatic analysis showed that the top three biological processes with the highest concentration of differentially expressed proteins were protein localization, the ERK1 and ERK2 cascade, and the response to organic cyclic compounds. Ingenuity pathway analysis shows the top action networks of proteins were albumin and ERK signaling pathways Western blot result shows higher expression levels of albumin and *p*-ERK in the ICH group

which inhibits oxidant-driven cultured neuronal damage caused by copper/ascorbic acid and hydrogen peroxide in vitro [22]. Additionally, bilirubin is transported via albumin. Evidence suggests that bilirubin can shield neurons from oxidative stress brought on by low-density lipoprotein cholesterol, which occurs frequently following ICH [23,24]. In ischemic stroke, higher level of oxidized serum albumin is correlated with better outcomes [25]. Amelioration of oxidative stress by albumin is possibly mediated by Wnt/β-catenin/ROS signaling [26].

4.4. Anti-inflammation

Evidence indicates that accessible thiol groups signal regulatory changes of inflammatory cells depending on their redox state [27]. Therefore, inflammation and oxidative stress are closely related. Low serum albumin concentrations can indicate a chronic inflammatory state. Inflammatory activation of macrophages and other immune system cells produces cytokines, including IL-1,IL-6 and tumor necrosis factor(TNF)-α, which will lead to a transformation of protein synthesis in the liver from albumin to other acute-phase proteins [28]. Albumin has been shown to enhance intracellular protection against inflammatory and oxidative stress damage via inhibiting TNF-α-induced upregulation of vascular cell adhesion molecule-1 (VCAM-1) and nuclear factor κB (NF- κB) in human aortic endothelial cells [29].

4.5. Anti-coagulation and anti-platelet

Albumin has an anti-thrombotic and anti-platelet effect, possibly dependent on its ability to bind nitric oxide (NO) to form S-nitrosothiols, thereby blocking the immediate inactivation of NO and allowing prolongation [30,31]. Hypoalbuminemia is associated with an increase in platelet aggregation, according to data from patients with nephrotic syndrome [30,32,33]. Of relevance is that intrahematomal blood clotting is a significant pathogenetic factor in perihematomal edema. During the first two days following ICH, the coagulation cascade is activated and thrombin is produced, which disrupts the blood-brain barrier permeability and promotes perihematomal edema [11].

4.6. Anti-apoptosis

The significant causes of neuron apoptosis in secondary brain injury in ICH are the release of thrombin, the toxic hematoma components and its degradation products, and the oxidative stress produced in perihematomal region [31,34]. Direct anti-apoptotic activity of albumin has been observed in human endothelial cells [35]. It has been demonstrated that free thiols of albumin play a significant role in determining the DNA-binding activity of active transcription factors such as NF- κB, thereby potentially influencing processes that determine cellular fate apoptosis [36].

5. Preclinical findings of albumin in animal ICH models

Albumin has consistently shown the potential as a neuroprotectant in preclinical settings. The effect of albumin is mostly studied in rat models using fresh or heparinized autologous blood injection. Albumin treatment significantly improves short and long-term neurologic function, protects BBB integrity, and reduces neuronal apoptosis and oxidative stress (Table 1). Several studies showed HSA treatment (25 % human albumin, 1.25 g/kg) significantly improve short-term neurobehavior within hours of treatment and throughout a 7-day survival. It remains beneficial to long-term neurological deficits on 28th dayafter ICH. However, there is no histological or MRI changes concerning hematoma volumes and brain swelling [37,38]. Two possible explanations exist for this observation. Firstly, behavioral assessments may be more effective in detecting improvement than histopathology. Secondly, the irreversibility of tissue loss due to hemorrhage distinguishes hemorrhagic stroke from ischemic stroke.

One study found that prompt HSA treatment significantly improved BBB integrity, as indicated by 49 % reduction in perihematomal Evans blue extravasation [38]. Another study demonstrated that albumin treatment significantly attenuated oxidative stress-mediated neuronal death, which may be partly via the ERK/Nrf2/HO-1 signaling pathway after ICH [39]. One quantitative proteomics study revealed that the albumin and ERK1/2 signaling pathways were the top protein-protein interaction networks [40]. Reich et al. found that albumin binds to EGF receptor and activates ERK in human renal epithelial cells and an important proximate event in the albumin-induced cell signaling was the production of ROS [41].

One study observed a considerable increase of albumin in the rodent brains of normoglycemic group but not in the brains of hyperglycemic group in response to ICH. Greater neuronal apoptosis was also observed in the perihematomal regions of hyperglycemic group. These observations suggest that the protective function of albumin in the acute stage of ICH may be a compensatory mechanism in response to blood glucose levels [42].

6. Clinical findings of albumin in patients with ICH

6.1. Independent prognostic value of serum albumin in ICH

Recent clinical evidence suggests that serum albumin concentration is an independent predicator of incident stroke and its subtype, hemorrhagic stroke (ICH). The Circulatory Risk in Communities Study (CIRCS) followed 5071 Japanese men and 7969 Japanese women aged 40 to 75. Low serum albumin levels were independently associated with an increased risk of total strokes, including

Table 2
Clinical findings of serum albumin level in ICH patients.

Reference	Design	Cohorts	Exclusions	Findings
[43]	prospective, observational	N = 13040 Serum albumin range (g/dL): Quartile 1: 2.6–4.2, Quartile 2: 4.3–4.4 Quartile 3: 4.5–4.6 Quartile 4: 4.7–5.6	a history of stroke, coronary artery disease, hepatic failure, kidney failure, or were undergoing hemodialysis at baseline	Low serum albumin levels were associated with an increased risk of intracerebral hemorrhage. (For the lowest vs. highest quartiles of serum albumin HR = 1.57, CI = 1.04–2.37))
[48]	Retrospective, observational	N = 2010 [subjects with hypoalbuminemia, n = 444; subjects without hypoalbuminemia, n = 1566 (Hypoalbuminemia was defined as total albumin≤3.5 g/dL)]	traumatic intracranial hemorrhage: brain lesions, such as intracranial tumor, aneurysm, or other vascular malformation presumed to be the cause of the bleeding; hemorrhagic transformation of acute ischemic stroke; missing data on infectious complications during hospitalization or missing data on long-term outcome	Hypoalbuminemia was an independent predictor of pneumonia (OR 1.76, 95 % CI 1.34–2.33, p \ 0.001) and sepsis (OR 2.29, 95 % CI 1.22–4.30, p = 0.010). Low levels of albumin were also independently associated with higher mortality at 90 days. (OR 1.78, 95 % CI 1.30–2.44, p \ 0.001).
[49]	Retrospective, observational	N = 639, serum albumin levels: Quartile 1:0.29–0.60, n = 154 Quartile 2:0.60–0.64, n = 164 Quartile 3:0.65–0.68,n = 159 Quartile 4: 0.69–0.83, n = 162	primary subarachnoid hemorrhage: hemorrhage caused by trauma, brain tumor, and transformation of ischemic stroke. Patients less than 18 years old, patients who had received anticoagulation or antiplatelet therapy, or patients who had severe liver disease, manifest liver-related syndrome, end-stage renal diseases, or hematologic diseases	Albumin were significantly different between groups for 90 day poor outcomes (mRS:3–6)by univariate analysis,however, disappeared after adjustment.
[47]	Retrospective, observational	N = 90 (normal serum albumin values n = 42; serum albumin levels below 3.4 g/dl, n = 48)	Patients <18 y ,without admission serum albumin levels	Although admission hypoalbuminemia did not have an impact on in-hospital mortality (28 vs 24 %, p = 0.635), it was a significant predictor of poor outcomes (death or discharge to a long-term nursing facility (mRS 4–6)) at discharge (59 vs 31 %, p = 0.009) (OR 3.2; 95 % CI; 1.3–7.8).
[50]	Retrospective, observational	N = 198 (survivor, n = 128; non-survivor, n = 70)	ICH due to vascular malformation, neoplasia, or trauma; presence of chronic acute and/or acute liver failure; evident hyperfibrinolysis; and age under 18 years.	The fibrinogen to albumin ratio is an independent early predictor of intrahospital mortality in neurosurgical ICU patients with ICH. An increased risk of intrahospital mortality was identified in ICH patients with a fibrinogen to albumin ratio greater than 0.075 upon admission.
[51]	Retrospective, observational	N = 149, Fibrinogen to albumin ratio levels: (Tertile 1[<8.06], n = 50; Tertile 2 [8.06–10.33], n = 48; Tertile 3[>10.33],n = 51	diagnosed with traumatic intracranial hemorrhage and subarachnoid hemorrhage; hemorrhagic infarction; extremely irregularity hematoma; cancer, severe hepatic disease [AST or ALT >5 times the upper limit of normal] and renal diseases [eGFR< 30 ml/min) or end-stage renal disease requiring dialysis; treated with defibrate or human albumin therapy.	Fibrinogen to albumin ratio on admission might be an independent predictor of hematoma enlargement after intracerebral hemorrhage. A significant difference in fibrinogen to albumin ratio between hematoma enlargement group and non-hematoma enlargement group (10.11 (8.37–11.73) vs 8.81 (7.61–10.39), p = 0.017).The highest tertile (>10.33) was independently related to hematoma enlargement (OR = 3.152, 95 % CI = 1.326–7.493, p = 0.009)
[52]	Retrospective, observational	N = 379 (survivor, n = 261; non-survivor, n = 118)	diagnosis of ICH due to trauma; vascular malformation or neoplasia; present of acute and/or chronic liver failure; age of <18 years.	An increase of 1 in the CRP/albumin ratio was associated with a 15.3 % increase in the risk of intra-hospital mortality (hazard ratio = 1.153, 95 % CI = 1.005–1.322, p = 0.42). A CRP/albumin ratio cut-off value greater than 1.22 was associated with increased intra-hospital mortality (Youden's Index = 0.19, sensitivity = 28.8, specificity = 89.9, p = 0.007).
[53]	Retrospective, observational	N = 518 (albumin < lower quartile, n = 130; albumin ≥ lower quartile, n = 388)	Bleeding due to brain tumors, vascular malformations, aneurysms, and trauma; patients who had undergone	Hypoalbuminemia was more frequent in ICH patients with SIRS (42 % versus 19 %; p < 0.001). Hypoalbuminemia was no longer significantly associated with

(*continued on next page*)

Table 2 (*continued*)

Reference	Design	Cohorts	Exclusions	Findings
			hematoma evacuation during their acute admission; age of <18 years.	the overall distribution of mRS score at discharge after adjustment. (adjusted common OR: 0.82, 95%CI, 0.52–1.29).
[54]	Retrospective, observational	N = 20 (Human albumin treated, n = 14 Furosemide treated, n = 6)	(1) had infections, cardiac, renal or liver disease, serum electrolyte disturbance, hypertension crisis; (2) had ICH related to trauma, coagulopathy, tumor, or arteriovenous malformation; (3) were less than 20 years of age or over 80 years old; (4) could not establish an accurate historical time of the stroke.	Of 14 patients with human albumin treatment, a decrease in the slowing activity was visually noted in 9 cases after the drug infusion. The spectral analysis demonstrated that albumin-induced EEG changes increased in alpha power and decreased in delta power in the lesion hemispheres, especially in the central and middle temporal areas. The effects occurred after 30 min and were maximal 1 h after the end of the infusion, then remained significant for 2 h post-infusion
[55]	Prospective. Experimental	N = 120 (control group, n = 40; impatient glycerol fructose use, n = 40; impatient albumin use, n = 40)	Not diagnosed as HICH; hematoma rupturing into the ventricular system and subarachnoid space; onset >24h; past history of ischemic stroke, acute or chronic cardiac and pulmonary disease	Compared with the glycerol fructose group, the volume of hematomas in the albumin group at 14 and 28 days was significantly reduced, the volume of the lesion around the hematoma at 7, 14 and 28 days was significantly reduced, and the score of neurological deficit was significantly improved (P < 0. 05), the blood IL-6 and TNF-α contents were significantly reduced, and the blood SOD activity and MDA content were increased (P < 0. 05)
[59]	Prospective, Experimental	N = 160 (control group,n = 40, Experiment group 1–3,n = 40)	Requiring surgical intervention; cerebellar or brainstem hemorrhage; with cerebral hemorrhage caused by arteriovenous malformation, aneurysm, malignant hematological disease, coagulation disorders, or brain tumors; patients with severe heart, liver, or kidney disease or systemic severe diseases; aged >65 or <36 years.	Compared with the control group, the total effective rate, hematoma volume and NIHSS score after treatment of each study group were all better than those of the control group(P < 0.05). Except for Study 1, the edema volume of study 2 or study 3 was smaller than that of control group (P < 0.05). The total effective rate, hematoma and edema volume, and NIHSS scores of study group 1 and group 2 or group 3 were significantly different (P < 0.05); There were no statistically significant differences of the evaluation indexes between study group 2 and group 3(P > 0.05).

Abbreviations: HR = hazard ratio; OR = odds ratio; CI = confidence interval; ICH-intracranial hemorrhage; mRS = modified Rankin Scale; HICH = hypertensive intracerebral hemorrhage; CRP: c-reactive protein; SIRS: systemic inflammatory response syndrome; SOD: super oxide dismutase; MDA = malondialdehyde.

ischemic stroke and ICH. After adjustment for traditional cerebrovascular risk factors, low serum albumin concentrations (< 4.3 g/dL) were associated with an increased risk of ICH [43]. Given the physiological characteristics of albumin, hypoalbuminemia may function as a modifiable risk factor.

It is well established that hypoalbuminemia (defined as a serum albumin concentration of less than 3.4 g/dL), a common occurrence in critically ill patients, is associated with poorer outcomes [44,45]. The prognostic relevance of serum albumin in cardiovascular and cerebrovascular diseases primarily attributable to malnutrition and inflammation [46]. The prognostic value, independent of well-defined risk factors and conventional prognostic markers, enlighten itsfunction in the progression and outcome of ICH (Table 2). In a single-center study consisting of 90 patients with spontaneous ICH, hypoalbuminemia at admission was a strong predictor of poor outcomes (defined as in-hospital death, transfer to hospice or nursing home placement) at discharge, independent of hepatic or renal dysfunction and other prognostic markers, whereas there is no impact on in-hospital mortality [47]. Additionally, a study of 2010 patients with ICH from 1994 to 2015 at the Massachusetts General Hospital supports the prognostic significance of serum albumin in ICH [48]. After adjusting for known predictors of outcome in ICH and other confounders, early hypoalbuminemia remained associated with an elevated risk of 90-day mortality. In the multivariate analysis, however, sepsis and pneumonia diminished the efficacy of the association. Early hypoalbuminemia was an independent predictor of pneumonia, sepsis, and infectious complications; therefore, infectious complications may be the biological mechanism by which hypoalbuminemia is associated with increased mortality, whereas the pathophysiology of inflammation and immunosuppression following ICH remains unknown.

Albumin is a negative acute-phase protein extensively studied in the prediction of inflammatory disease, when combined with other positive acute-phase proteins, may serve as a novel serum biomarker in ICH. The acute-phase protein fibrinogen is an essential part of

the coagulation system and also drives and induces systemic inflammation. The fibrinogen to albumin ratio upon admission, as an early inflammatory serum biomarker, has been identified to independently predict hematoma enlargement and in-hospital mortality in neurosurgical ICU patients with ICH [50,51]. In addition, C reactive protein (CRP) is an easily available positive acute-phase protein and increases following infection, ischemia, and/or trauma [56,57]. CRP to albumin ratio greater than 1.22 upon admission was also regarded as a new independent predictor of in-hospital mortality in patients with ICH [57–59]. The CRP/albumin ratio was developed to integrate information regarding the relation between systemic inflammation, dystrophy, and nutritional condition in a new biomarker [56,57].

Nevertheless, there are still few observations indicating negative or inconclusive results with its prognostic value. One study with a total of 639 spontaneous ICH patients focusing on the association between liver function indicators and outcomes found the association between albumin and 90-day poor outcome (modified Rankin Score 4–6) inin the univariate analysis whichdisappeared after adjustment in multivariate analysis [49]. Another multi-center and multinational cohort study (n = 518) from MNEMONICH database aimed to examine the relationships between systemic inflammatory response syndrome (SIRS), serum albumin concentrations and ICH outcomes [53]. When SIRS was accounted, predictive effect of serum albumin was inevident, which suggests serum albumin levels may simply be a marker for identifying SIRS-positive ICH patients with high risk of poor functional outcome and in-hospital mortality, instead of a possible therapeutic target.

6.2. Potential therapeutic implications of serum albumin in ICH

From a clinical and therapeutic point, there is no sufficient evidence to prove albumin administration in patients with ICH. In a study characterizing alterations in continuous EEG monitoring [54], 20 patients were administrated 20 % HSA 50 ml and monitored for 3h before and after drug infusion. The spectral analysis demonstrated that albumin-induced EEG changes increased in alpha power and decreased in delta power in the lesion hemispheres, especially in the central and middle temporal areas. Albumin evidently improves abnormal EEG in cases with hemorrhage and mass effects in the CT scans, suggesting the action is possibly mediated by lowering intracranial pressure and dehydrating brain edema. One controlled trial found that HSA treatment (20 g/d for 10d) in addition can reduce the volume of hemorrhage and surrounding edema. It can also lower the expression levels of IL-6 and TNF-α in the blood, increase SOD activity and decrease the amount of MDA in the blood, thus decreasing brain parenchymal loss and achieving clinical improvement [55]. Another controlled trial found combination of mannitol, human albumin and furosemide can more effectively reduce edema and hematoma volume, compared.

th the treatment of reducing ICP with mannitol alone [59].

Albumin for ICH Intervention (ACHIEVE) [NCT00990509], a single-center, randomized, phase 2 trial aims to evaluate the positive and negative effects of albumin in patients with ICH within 24 h of symptom onset with the primary outcome measure being the frequency and severity of blood brain barrier disruption based on pre- and post-contrast MRI. Nevertheless, it was terminated due to poor enrollment. In addition, a meta-analysis of 55 randomized controlled trials as well as a Cochrane systematic review concluded that there was no evidence that albumin administration reduces mortality in critically ill patient [60,61].

6.3. Potential adverse effects of serum albumin in ICH

6.3.1. Pulmonary edema

Life-threatening pulmonary edema occurs when there is an excessive loss of protein and fluid from blood vessels, which cannot be evacuated by the lymphatics from the interstitial space. This happens when capillary walls become more permeable due to diseases or tissue damage, causing an increase in fluid and protein leakage into the interstitial space that cannot be matched by lymphatic drainage. Furthermore, a drop in hydrostatic pressure in the interstitial space can further increase the filtration rate. Albumin is administered to maintain intravascular volume in these patients [60]. However, due to the increased vessel permeability, albumin solution is ineffective at maintaining plasma volume compared with individuals with normal vessel permeability. Thus the rationale for administering albumin solutions becomes more uncertain. Some research, however, suggests that albumin does not persist in the interstitial compartment and contributes to edema. A critical illness affects both the rate of albumin synthesis and degradation, as well as the transcapillary escape rate (TER) and lymph flow, leading to hypoalbuminemia and altered distribution. Albumin supplementation increases intravascular oncotic pressure and reestablishes the transcapillary oncotic pressure gradient in conditions characterized by decreased oncotic pressure [62].

6.3.2. Anti -coagulation

Albumin is believed to have anticoagulant properties as mentioned before, while such anticoagulant activity may be harmful in critically ill patients, especially those with hemorrhagic hypovolemia. In Albumin in Acute Stroke(ALIAS) trial part two, the authors suggest that the increased rate of transformation to symptomatic ICH(sICH) is primarily related to endovascular thrombolysis and albumin's effect on anti-platelet aggregation and collateral perfusion [63]. The increased rate of sICH in ALIAS 2 was non-significant, but it remains a possible concern.

6.4. Barrier and roadmap to trialing albumin treatment in human ICH

Although the putative mechanisms of secondary injury in ICH and ischemic stroke differ somewhat, there is certainly substantial overlap, and the neutral outcome in the ALIAS part I and 2 studies present a near-insurmountable barrier to trialing albumin treatment

in human ICH.

The ALIAS study was an international randomized placebo-controlled trial of albumin. The part 1 of the study was terminated early due to a correlation between pulmonary edema and premature mortality (particularly in elderly patients and those receiving large amounts of intravenous fluids) [64]. As a consequence, the protocol was modified to impose restrictions on fluid consumption, age, and the use of diuretics. However in ALIAS part two, albumin treatment was still associated with an increase in pulmonary edema [63]. Given this, it is difficult to conceive how administering albumin could ever compensate for the deficiency without causing additional complications. Consequently, it is premature so far to call for prospective research of albumin therapy in human.

The roadmap to translating positive preclinical results into beneficial outcomes in human patients should start with understanding the precise pathophysiology, andoptimizing dosages, timing of administration. The failure of the previous hypothesis that albumin might be a neuroprotectant in ischemic stroke has been ascribed to delayed treatment [65], so the time window for recruitment after ICH onset should be carefully considered in the future clinical trials. Second, standardizing animal models to reflect patients' comorbidities, age, and site of injury may reduce translational bias. Animal models of ICH have been instructive, but they have limitations. Most data from ICH models are from healthy, young animals that cannot represent the older age and common morbidities of human ICH population, for example, distinct levels of oxidative stress and neuroinflammatory response [66,67]. Third, incorporating standardized outcome measures, such as imaging, will facilitate comparability. Fourth, at the heart of clinical controversy surrounding the use of hypoalbuminemia as an outcome predictor is the question of causality – whether hypoalbuminemia directly contributes to poor outcomes, in which case albumin administration may improve outcomes, or merely serves as a marker for poor outcomes. Unidentified confounding variables may exist, such as increased perihematomal edema, heart failure, or other cardio-pulmonary and renal complications [68].

7. Conclusions

In this review, we summarized the potential neuroprotective and prognostic values of albumin in the preclinical and clinical settings of spontaneous ICH. Albumin-mediated neuroprotection in rodent models stems from its biological functions, including its major anti-oxidation activity, anti-inflammatory responses, and anti-apoptosis. Nevertheless, it has been inconclusive in the transition to clinical trials. The potential adverse effects of albumin therapy, the possibility of volume overload, and the subsequent pulmonary edema in ICH patients cannot be neglected. Given the demonstrable potential harm in ALIAS I and II, cohort studies seem unwarranted so far.

Understanding the intricate effects of albumin on acute brain injuries has significant clinical implications. As a prognostic marker and treatment, albumin serves a crucial role in neurocritical care. However, the use of albumin has been ambiguous due to the varying conclusions of clinical studies, the absence of precise guidelines, and common misconceptions. Therefore, more preclinical evidences are required, and prospective clinical trials of albumin therapy are premature at this time.

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