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Biomarkers as outcome predictors in subarachnoid hemorrhage – a systematic review

Caron M. Hong[1], **Cigdem Tosun**[2], **David B. Kurland**[2], **Volodymyr Gerzanich**[2], **David Schreibman**[1], and **J. Marc Simard**[2,3,4]

[1]Department of Anesthesiology, Division of Critical Care Medicine, University of Maryland School of Medicine, Baltimore, MD, USA

[2]Department of Neurosurgery, University of Maryland School of Medicine, Baltimore, MD, USA

[3]Department of Pathology, University of Maryland School of Medicine, Baltimore, MD, USA

[4]Department of Physiology, University of Maryland School of Medicine, Baltimore, MD, USA

Abstract

Context—Subarachnoid hemorrhage (SAH) has a high fatality rate and many suffer from delayed neurological deficits. Biomarkers may aid in the identification of high-risk patients, guide treatment/management and improve outcome.

Objective—The aim of this review was to summarize biomarkers of SAH associated with outcome.

Methods—An electronic database query was completed, including an additional review of reference lists to include all potential human studies.

Results—A total of 298 articles were identified; 112 were reviewed; 55 studies were included.

Conclusion—This review details biomarkers of SAH that correlate with outcome. It provides the basis for research investigating their possible translation into the management of SAH patients.

Keywords

Biomarkers; critical care; markers; outcome; subarachnoid hemorrhage; vasospasm

Introduction

Subarachnoid hemorrhage (SAH) comprises about 5% of all strokes (Ostrowski et al., 2006). The mortality from this devastating condition is high, with a case fatality rate of about 50% (Hop et al., 1997), with more than 30% of patients dying from the initial hemorrhage or rehemorrhage (Ostrowski et al., 2006). Of those who survive, more than 40% have long-

Address for correspondence: Dr Caron M. Hong, Department of Anesthesiology, University of Maryland School of Medicine, 22 South Greene Street, S11C, Baltimore, MD 21230, USA. Tel: 410-328-6120. chong@anes.umm.edu.

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term delayed neurological deficits (DNDs), including stroke, cognitive and neuropsychological abnormalities that adversely affect overall function and quality of life. The multi-faceted pathophysiology of SAH, combined with poor functional outcome, underscores the need for prognostic serum biological markers that can be used to aid in the identification of patients at high-risk for vasospasm, ischemia and stroke *prior* to neurological deterioration.

A number of factors contribute to DNDs and poor outcome after SAH including cerebral vasospasm, ischemia, stroke, microthrombi, oxidative damage and inflammation (Kassell et al., 1985). Of these, vasospasm has been the most widely researched. Although it is a common, potentially treatable, complication of SAH, its pathogenesis is not completely understood. Results from the CONSCIOUS trials (Macdonald et al., 2008, 2010, 2011, 2013; Meyers & Connolly, 2011) demonstrated that the prevention of angiographic vasospasm has equivocal effects on outcome. This finding has led to a reevaluation of the pathogenesis of brain injury in SAH and a resurgence of interest in neuroinflammation as a primary culprit. Neuroinflammation, vasospasm, ischemia and stroke may be interdependent manifestations of a worsening clinical course.

Parameters associated with outcome in SAH assess the state of the patient on admission and include age, admission neurologic grade (i.e. Hunt and Hess grade and World Federation of Neurological Surgeons grade) and the amount of blood on admission computed tomography (CT) scan (i.e. Fisher grade or similar classification). The current management of SAH patients, during the acute phase of the disease process, is centered on identifying changes in neurological examination or imaging studies, such as CT or transcranial Doppler (TCD). Imaging studies are performed either routinely or are obtained following changes in clinical signs or symptoms. Imaging that are triggered by patient decline, and preemptive medical treatment that is often initiated before imaging, results in appropriate management for some patients, but for others, can result in unnecessary treatment and multiple unnecessary imaging studies. Medical treatment of SAH is not without risk and can increase morbidity, length of hospital stay and mortality (Suarez et al., 2006). 40% of SAH patients experience medical complications including pulmonary edema, cardiac arrhythmia and electrolyte disturbances (Solenski et al., 1995; Suarez, et al., 2006). These complications are secondary to the treatment and the nature of the disease. Irregardless, utilizing prognostic serum biomarkers to aid in predicting which patients will have neurological sequelae before symptomatic presentation may help guide treatment during the acute phase, would allow for standardized monitoring that could identify high-risk patients and initiate early therapy prior to clinical deterioration. This approach could also improve cost effectiveness, decrease unnecessary treatment, reduce the need for emergent imaging, and ultimately improving patient care and outcome after SAH.

Biomarkers are a measurable entity representing a biological or pathophysiological process. Some serum biomarkers have proven to be reliable tools for diagnosis, therapeutic decision making and prognosis in many disease states. Prominent examples of utilization of biomarkers in medicine include the use of cardiac troponin I (cTnI) for acute myocardial infarction, B-type naturetic peptide for congestive heart failure and C-reactive protein (CRP) and lactate for septic shock. Although the kinetics of each biomarker of outcome in SAH is

beyond the scope of this review, this article aims to focus on the evidence-based research and potential utility of these biomarkers in the prognosis of patients after SAH. This systematic review summarizes biomarkers that have been specifically associated with clinical outcome, focusing on serum biomarkers, in hopes of providing an impetus for further research towards the development and implementation in the management of SAH patients.

Methods

MEDLINE (1946–January 2013), PubMed (1809–January 2013) and EMBASE (2009–January 2013) electronic databases were queried. The search included the medical subject heading and keywords “subarachnoid hemorrhage” AND “biomarkers” AND “outcome”. There were no restrictions in language. The initial search identified 252 potentially usable studies. An extensive detailed review of reference lists was done to include all potential studies, as not all study results were identified as “biomarkers” of SAH. This resulted in 46 additional studies. A total of 298 studies resulted. All duplicates were eliminated. The remaining studies were reviewed by the authors for inclusion via abstract review. 72 publications were excluded by abstract review secondary to no outcome analysis. Of the remaining 112 studies, 57 studies were excluded after manuscript review by the primary author, and confirmed by all other authors. These included studies with no direct association with outcome after SAH, animal studies, editorial/reviews and imaging used as a “biomarker”. A total of 55 studies were retained and included in this systematic review (Figure 1). All 55 articles were agreed by all authors to support the goal of this review, identifying biomarkers that have been directly associated with outcome after SAH.

Results

Manual abstract screening and exclusion of articles were completed as describe above. All the studies included in this review were human and written in English. There were a significant amount of studies identified from the detailed reference list review. These studies did not specifically state their findings were “biomarkers” and therefore were not found on the initial search. A total of 46 additional studies resulted. A summary of studies included in this systematic review is given, by group, in Table 1.

There were a number of variabilities within these studies including the study size, the timing of assessment of outcome, the outcome scoring scale used and the substrate tested. The study sizes varied from 20 to 378 subjects. There was short-term and long-term timing for assessments of outcome. This included 3–12 days after SAH, discharge from hospital and 1 month to 1 year after SAH. There was also a variety of outcome scoring scales used included Glasgow Outcome Scale (GOS), Glasgow Outcome Scale Extended (GOSE), Mini-Mental State Examination (MMSE), Rankin Disability Index (RDI), modified Rankin Score (mRS), modified Tardieu Scale (mTS) and the Barthel Index (BI). Tested substrates include blood, CSF and brain tissue (microdialysis). Direct comparisons between the studies were not done for this systematic review secondary to such variabilities, however discussed below are cited sensitivities and specificities.

A biomarkers' ability to accurately determine negative and positive subjects will guide their utility in clinical practice. In SAH, acceptable sensitivities and specificities were demonstrated with CRP, selectin, thrombin antithrombin complex (TAT), creatine kinase-BB (CK-BB) and malondialdehyde (MDA) (83 versus 84%, 90 versus 83%, 72 versus 70%, 70 versus 100% and 88 versus 75%, respectively) (Coplin et al., 1999; Jeon et al., 2012; Kaneda et al., 2010; Morga et al., 2007; Wang et al., 2011). Although most of the sensitivities and specificities are not greater than 90%, each of these markers may be able to identify subjects that have poor outcome and those that will potentially recover well with some reasonableness.

Some biomarkers have acceptable sensitivities but poor specificities. These included GFAP, neurofilament, ubiquitin C terminal hydrolase 1 (UCHL1) and D-dimer (92 versus 40%, 40–100% versus 14–91%, 90 versus 50%, 88 versus 36%, respectively) (Lewis et al., 2010; Morga, et al., 2007; Nylen et al., 2007; Petzold et al., 2006). Microalbuimuria had a poor sensitivity but an acceptable specificity (60 versus 96%, respectively) (Terao et al., 2007). Surprisingly, although S100β had the most number of studies secondary to the logical promise of its utilization, a study demonstrated poor sensitivity and specificity with outcome, 50 and 67% respectively (Weiss et al., 2006). In this review, we discuss biomarkers of SAH and the evidence of their applicability to outcome.

Discussion

Neuron and astrocyte specific markers

Central nervous system (CNS)-specific markers have been the focus of research as potential biomarkers for outcome after SAH, specifically markers originating from neurons and astrocytes. S100β, neuron-specific enolase (NSE), glial fibrillary acid protein (GFAP), apolipoprotein E (apoE) and APOE gene, neurofilament, amyloid β-protein and ubiquitin C terminal hydrolase 1 (UCHL1) have been studied. Of these, S100β has been used as a prognostic adjunct tool, monitoring outcome following therapeutic treatment with magnesium and atorvastatin in SAH patients (Hassan et al., 2012; Schmid-Elsaesser et al., 2006).

S100β—S100β is a group of calcium-binding protein dimers found predominantly in astrocytes, glial and Schwann cells in the CNS. It is released secondary to pathological brain injury such as SAH, acute brain injury, traumatic brain injury (TBI), acute ischemic stroke and cardiac arrest reflecting neuroinflammation and injury. Increased blood levels of S100β are associated with brain injury in TBI (Ingebrigtsen et al., 1999; Kanner et al., 2003) and stroke (Kanner et al., 2003), and has demonstrated some validity in SAH. In 1998, Persson et al. (1988) were among the first to demonstrate high cerebral spinal fluid (CSF) levels of S100β after SAH. Concentrations were related to the severity of hemorrhage, the development of delayed ischemia secondary to vasospasm and outcome. Since this early study, the relationship between S100β and vasospasm has been controversial. Moritz et al. (2010) and Jung et al. (2013) demonstrated no association with increased S100β levels and vasospasm. Interestingly, Herrmann et al. (2000) found that patients with strokes that had low blood levels of S100β completely recovered, with reversible pathology. This correlated

with finding by Jung et al. (2013) who demonstrated a similar association in SAH. They showed that patients with vasospasm and no elevation of S100β had no delayed cerebral ischemia.

More recently, Sanchez-Pena et al. (2008) demonstrated that the mean 15-day S100β blood level is a prognostic indicator of 12-month outcome in SAH. Few studies that have investigated S100β in CSF found a similar correlation with outcome (Hardemark et al., 1989; Kaneda et al., 2010). CSF sampling is difficult to collect and exposes the patient to additional risks. Therefore, serum sampling would be more efficacious and safe in comparison. S100β may be a prognostic biomarker of SAH, and brain injury in general, specifically with the potential to identify patients with reversible injury. Further research must focus on its efficacy in guiding the management of SAH, identifying appropriate high-risk patients and its impact as a prognostic tool in SAH.

Neuron-specific enolase—Neuron-specific enolase (NSE) is a cytoplasmic enzyme released by neurons and neuroendocrine cells after damage to the CNS. Although NSE has been shown to increase with SAH, there have been controversial results regarding its associations with outcome Kacira et al. (2007) demonstrated an increase in CSF and blood NSE levels after SAH. Kaneda et al. (2010) and Oertel et al. (2006) found no correlation with CSF or blood NSE levels with outcome, respectively. Mortiz et al. (2010) investigated both CSF and blood NSE and found a correlation with CSF only. Mabe et al. (1991) demonstrated a significant correlation with serum NSE and outcome. The studies demonstrating an association with NSE and outcome determined Glasgow outcome scale (GOS) at discharge from the intensive care unit or hospital (Mabe et al., 1991; Moritz et al., 2010). Therefore, NSE may be a biomarker of prognosis in the acute phase after SAH, as there was no correlation with 6-month outcome (Oertel et al., 2006).

Glial fibrillary acid protein—Glial fibrillary acid protein (GFAP) is a cytoskeleton protein that serves as an intermediate filament in mature astrocytes. It is increased in CSF in brain pathologies such as stroke, intracerebral hemorrhage, dementia and SAH and has been associated with predicting functional outcome after stroke and TBI (Herrmann et al., 2000; Mondello et al., 2011, 2012). Vos et al. (2004) concur that GFAP levels in blood are a prognostic indicator of functional outcome after stroke and TBI. In SAH, although there are no studies demonstrating a direct association with GFAP and vasospasm, there are three studies that demonstrate GFAP as an independent predictor of poor outcome (Kaneda et al., 2010; Vos et al., 2006) as far out as 1 year (Nylen et al., 2007). Although Vos et al. (2006) demonstrated that both S100β and GFAP in blood were associated with increased odds for poor outcome at hospital discharge, S100β was a better predictor. This differentiation may be due to the timing of release after injury, level of vasogenic edema, cytotoxicity and apoptosis after SAH. Regardless, GFAP shows promise as a marker of outcome in SAH. Further research is required for validation and applicability.

Apolipoprotein E (ApoE)—ApoE is a polymorphic protein produced in the brain that exerts neurotrophic and neuroprotective effects. It has been linked to neurological disease states such as TBI and Alzheimer's disease (Lanterna & Biroli, 2009). The biological effects of ApoE after SAH include modulation of inflammation in the brain, free radical scavenger,

membrane repair, excitotoxicity protection, protection against apoptosis and smooth muscle contraction (Lanterna & Biroli, 2009). In SAH, decreased CSF levels of ApoE correlate with poor outcome (Kay et al., 2003a). Moreover, an ApoE-mimetic peptide, derived from the receptor binding site of the protein, demonstrated therapeutic benefit in a mouse model, improving functional outcome, reducing mortality and decreasing vasospasm (Gao et al., 2006).

The APOE gene has been associated with outcome and delayed cerebral ischemia after SAH. In a more than 10-year longitudinal study, Louko et al. (2006) demonstrated that, although not statistically conclusive, carriers of the E4 isoform had a greater risk for impaired memory and color naming. However, Morris et al. (2004) demonstrated no significant association between E4 carriers and cognitive impairment. Although APOE, specifically the E4 isoform, has been shown to be associated with mortality and poor outcome (Dunn et al., 2001; Gao et al., 2006; Kay et al., 2003a,b; Lanterna et al., 2005; Leung et al., 2002; Louko et al., 2006; Niskakangas et al., 2001; Tang et al., 2003), data supporting its use as a biomarker for prognosis are weak. Furthermore, the absolute (positive or negative) value of genotyping, and the inability to identify abnormal elevations or depressions, limits the potential usefulness in monitoring the progression of disease in SAH.

Others—Other neuronal-specific biomarkers that have been associated with outcome in SAH are neurofilament (NF), amyloid β-protein and ubiquitin C terminal hydrolase 1 (UCHL1). All three markers reflect a level of brain injury or degeneration and have been associated with poor outcome (Kay et al., 2003b; Lewis et al., 2010; Nylen et al., 2006; Petzold et al., 2006). Neurofilament is a structural component of motor axons and a marker of neuronal injury in white matter. There are three studies demonstrating that elevated levels of neurofilament in CSF is associated with outcome in SAH (Lewis et al., 2010; Nylen et al., 2006; Petzold et al., 2006) as far out as 1 year (Nylen et al., 2006). However, Zanier et al. (2011) demonstrated no correlation with neurofilament CSF levels and adverse events or long-term clinical outcome. Amyloid β-protein activates enzymatic processes, protects against oxidation and is a transcriptional factor. Kay et al. (2003b) demonstrated, in a small human study, that decreased levels of CSF amyloid β-protein correlated with poor clinical outcome at 3 months. UCHL1 is an enzyme specific to neurons and neuroendocrine cells and is concentrated in dendrites in gray matter, representing 1–2% of human brain protein. It is released into the CSF following neuronal and dendritic injury. Lewis et al. (2010) demonstrated that increased levels of CSF UCHL1 for more than 10 days post-aneurysm rupture were predictive of poor outcome. The research on these three markers is in its infancy and further work must be done to determine systemic correlations and their possible utility as predictors of outcome in SAH.

Inflammatory biomarkers

Inflammation plays a key role in the pathology of SAH and contributes to functional and cognitive outcome. In SAH, the action of blood in the subarachnoid space initiates the rapid activation of inflammatory cascades that include vascular and cellular components, such as leukocyte migration and cell adhesion molecules in endothelial cells. This initial, acute,

neuroinflammatory response plays an important role in the treatment and prognosis of patients with SAH.

A number of cytokines, proinflammatory markers and products of metabolism have been correlated with poor outcome after SAH. These include C-reactive protein (CRP), TNF-α, IL-1 family members (i.e. IL-1 receptor antagonist: IL-1Ra), IL-6, IL-8, high-mobility group box 1 protein (HMGB1), catecholamines and microalbuminuria. Other serum markers such as procalcitonin (PCT) and myeloperoxidase (MPO) have not been demonstrated to be associated with outcome, but have been associated with inflammation in SAH (Cengiz et al., 2007; Kofoed et al., 2007; Luzzani et al., 2003; Oconnor et al., 2004; Reinhart & Meisner, 2011). Lactate, a product of anaerobic metabolism, is a biomarker of mortality in patients with septic shock (Manikis et al., 1995; Mikkelsen et al., 2009). In SAH, lactate has been associated with poor outcome in a mouse model (Cengiz et al., 2007); however, no human studies have been reported.

C-reactive protein—C-reactive protein (CRP) is a member of the acute phase reactant protein family and has been used as a prognostic biomarker in bacterial infection and sepsis. CRP is produced by hepatocytes secondary to cytokine and inflammatory stimulation. It is one of the most widely used marker of infection in the critically ill, with varying levels of sensitivity and specificity (Vincent et al., 2011). When used in combination with other markers of infection, such as temperature, there is an increased specificity and sensitivity. CRP is a marker of inflammation after SAH and has been associated with vasospasm and poor outcome. The study by Fountas et al. (2009) was the first to investigate CRP and its association with outcome in SAH, and is the only study that assessed both blood and CSF levels of CRP. They showed that elevated CRP was associated with vasospasm and less favorable outcome at discharge, with a peak on post-admission day 3. Within the past few years, many investigators have concurred that CRP is a marker of poor outcome in SAH patients. Badjatia et al. (2011) demonstrated that elevated high sensitivity CRP (hsCRP), in the first 14 days after SAH, is an independent predictor of delayed cerebral ischemia. Kubo et al. (2008) additionally demonstrated that elevated hsCRP, at day 0 and day 7, was associated with delayed ischemic neurological deficits. Romero et al. (2012) demonstrated that elevated blood levels of CRP were associated with less favorable prognosis on discharge and that CRP blood levels were related to severity of SAH. Frontera et al. (2012) concurred showing that CRP blood levels were significantly higher in poorer grade patients over time and correlated with severity of SAH on admission. Jeon et al. (2012) demonstrated specifically in surgical SAH patients, that pre-operative and post-operative blood levels of CRP were associated with poor outcome. In this study, postoperative day 1–2 elevated CRP levels were associated with severe neurological deterioration on admission, cerebral infarction, intracerebral hemorrhage and surgical decompression.

Although the above mentioned data supporting the potential utility of CRP as a prognostic serum biomarker in SAH is mounting, it is important to recognize that CRP is not specific for neurologic injury. CRP is a marker of a systemic inflammatory response and is not produced by brain tissue. It is uncertain if it enters the brain and contributes to the pathogenesis of cerebral tissue damage or if it is a systemic marker of the severity of SAH. In addition, it is common to have a secondary process, pneumonia or another infective

process, during the acute phase after SAH that may confound the sensitivity and specificity of CRP. Nevertheless, CRP has been shown to be a useful predictive indicator of outcome, making it an appealing measure in SAH.

Cytokines—TNF-α and IL-6 are acute phase reactant cytokines produced by a number of cells in response to inflammatory stimulus. IL-1β is a proinflammatory cytokine that is produced by activated macrophages. IL-1Ra is an antiinflammatory cytokine, which is also a part of the milieu of acute phase reactants produced by immune cells and hepatocytes. However, its role in the inflammatory process is unclear. IL-8 is a neutrophil chemotactic factor that is produced by a number of cells, including macrophages and endothelial cells, after a stimulus. Increased levels of these cytokines have been associated with poor outcome in SAH (Chou et al., 2012; Fassbender et al., 2001; Mathiesen et al., 1997; Nakahara et al., 2009; Sozen et al., 2009). The role of TNF-α and IL-6 in the acute phase of inflammation after SAH is well documented. However, few studies have looked at their association with outcome. Chou et al. (2012) demonstrated an association between serum TNF-α and a poor outcome at 6 months after SAH. Sozen et al. (2009) demonstrated that inhibition of IL-lβ in a mouse model of SAH reduced mortality and improved neurological function. However, there are no human studies investigating outcome and IL-1β in SAH. Mathiesen et al. (1997) demonstrated that levels of IL-1Rα and TNF-α were increased after SAH and were associated with unfavorable outcome at 12 days post-SAH. Fassbender et al. (2001) demonstrated that increased CSF IL-6 levels were significantly associated with poor outcome. Nakahara et al. (2009) showed increased levels of IL-8 in blood were associated with unfavorable outcome. These primary studies provide a basis for the potential use of these neuroinflammatory biomarkers as prognostic markers in SAH.

Importantly, the levels of cytokines in CSF and blood are not equivalent. Inflammatory markers peak initially in the CSF with a variable delayed secondary peak in the blood. This variable secondary peak of blood cytokines must be further investigated, as blood is the most practical source for sampling. As with any marker of inflammation, patients having a concurrent inflammatory or infectious process in addition to SAH may have “non-specific” elevations in cytokines.

Catecholamines and other products of metabolism—SAH initiates a profound neuroinflammatory response, including a centrally-mediated sympathetic response. Moussouttas et al. (2012) and Dilraj et al. (1992) demonstrated that plasma and CSF levels of epinephrine are independent predictors of morbidity and mortality in SAH. Although epinephrine detection assays of blood and urine are well-developed and simplistic, epinephrine should be combined with other markers of disease to increase sensitivity and specificity for SAH.

Microalbuminuria is a product of metabolism and a biomarker of infection and sepsis. It corresponds to a low rate of albumin excretion in the urine and is a non-specific marker of inflammation associated with increased vascular permeability and is measured as an albumin/creatinine ratio. Terao et al. (2007) found a microalbumin/creatinine ratio greater than 200 mg/g to be a potent independent predictor of unfavorable neurological outcome.

Although non-specific, this biomarker has potential as it has successfully been utilized in other inflammatory disease states.

Molecular adhesion and extracellular matrix markers

Early brain injury after SAH involves the contraction of cerebral arteries resulting in the release of several vasoactive factors that may lead to endothelial cell damage and vasospasm. Intimal proliferation is a consequence of disturbed endothelial cells that can last up to 2 weeks after the onset of SAH. Molecular adhesion and extracellular matrix proteins are critical in this process and are associated with outcome in SAH. These proteins include matrix metalloproteinase-9 (MMP-9), intracellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and L-selectin. They are intimately involved with the vasculature and acute pathogenesis of disease, signifying the potential for use as biomarkers in SAH.

Matrix metalloproteinase-9—Matrix metalloproteinase-9 (MMP-9) is an extracellular matrix protein predominately released by neutrophils after brain injury secondary to ischemia and neurodegenerative disorders. It is one of the first factors to be prominently upregulated in smooth muscle cells and leukocytes that can account for the onset of myeloproliferative intimal lesions leading to vasospasm in SAH. MMP-9 plays a key role in the pathophysiology of acute brain injury in SAH as it (1) breaks down the blood brain barrier, (2) enhances cerebral edema and (3) facilitates neuronal and vascular apoptosis. McGirt et al. (2002) showed an increase in serum MMP-9 was associated with vasospasm. Chou et al. (2011) demonstrated an increase in blood and CSF MMP-9 levels were associated with poor clinical outcome at 3 months, but not with vasospasm. These studies demonstrate the potential of serum MMP-9 as a prognostic biomarker in the acute phase of SAH.

Intracellular adhesion molecule-1 and vascular cell adhesion molecule—Adhesion molecules have long been implicated in mediating a robust inflammatory response following an ischemic insult. Intracellular adhesion molecule-1 (ICAM-1) is expressed at low concentrations in endothelial cells and leukocytes under normal physiological conditions. However, with inflammatory stimuli, ICAM-1 activates an inflammatory cascade that may lead to vasospasm. The adherence of leukocytes to the vascular endothelium is a hallmark of inflammation and is induced by these adhesion molecules. Elevated serum ICAM-1 levels have been correlated with poor clinical outcome (Kaynar et al., 2004; Kubo et al., 2008; Mack et al., 2002). Kaynar et al. (2004) have postulated that simultaneous release of soluble ICAM-1 and vascular cell adhesion molecule-1 (VCAM-1) in CSF and blood are risk factors for unfavorable outcome and post-hemorrhagic vasospasm. These adhesion molecules can serve as serum biomarkers of outcome for SAH and may be the basis of specific antibody inhibition that may improve functional outcome.

Selectin—Selectin is another cell adhesion molecule family. There are three main types, depending on origin, endothelial (E), platelets (P) and leukocytes (L). Mean serum P- and L-selectins in SAH patients are associated with an onset of delayed ischemic neurologic deficits (Nissen et al., 2000). However, only L-selectin, was associated with poor outcome

(Wang et al., 2011). This is a single study, demonstrating an opportunity for further investigation.

Biomarkers of the vasculature and clotting cascade

The search for markers of brain injury and neurological deficits in the setting of SAH has been heavily focused on vascular components and the clotting cascade. This is largely a consequence of the research emphasis on vasospasm and the associated clinical deterioration. The results from the CONSCIOUS-2 trial (Macdonald et al., 2013), which showed that prevention of angiographic vasospasm had equivocal effects on outcome, has led to a reevaluation of the pathogenesis of brain injury in SAH. However, these findings do not discount endothelin-1 (ET-1) as a potential biomarker for SAH, as it parallels vasospasm, an independently strong indicator of worsening clinical status. A detailed discussion of vasospasm, and its prognostic biomarkers, is beyond the scope of this review. However, ET-1 warrants some discussion. Several lines of evidence have implicated ET-1 in the pathogenesis of vasospasm: (1) ET-1 is a very potent vasoconstrictor (Webb et al., 1998), (2) ET-1 is found in elevated quantities in CSF and blood in SAH patients (Masaoka et al., 1989; Suzuki et al., 1990), (3) ET-1 can evoke vasospasm experimentally (Zubkov et al., 2000) and (4) specific antagonists of ET-1 attenuate angiographic vasospasm in experimental SAH (Juvela, 2000). Production of ET-1 has been attributed to endothelial cells, smooth muscle cells, neurons, astrocytes and CSF leukocytes (Fassbender et al., 2000). Seifert et al. (1995) have shown that ET-1 levels are strongly predictive of hematoma volume and development of delayed neurological deficits.

Inasmuch as vasospasm is an independent marker of worsening clinical course, serum biomarkers of vascular injury and coagulation upregulation may be of clinical use. A more thorough understanding of these biomarkers, and the signaling cascades involved, may lead to their development and implementation into the clinical management of SAH and novel therapeutic options for this devastating disease.

Endothelial cell activation and microparticles—Markers relating to endothelial cell damage or activation may be among the most specific early markers relating to SAH. Fibronectin containing extra type III domain (ED1-fn) is a sensitive marker of endothelial cell activation in SAH and is increased 72 hours after SAH (Frijns et al., 2002). ED1-fn is associated with the clinical condition on admission, and is increased in delayed cerebral ischemia. Regardless of whether endothelial cell activation is a consequence or a cause of delayed cerebral ischemia, activated endothelial cells may be involved in other aspects of SAH-related injury. A recent study by Lackner et al. (2010) looked at levels of endothelial microparticles in SAH, as a measure of endothelial cell damage. In patients with any level of disability (modified Rankin Scale ≥1), microparticles were elevated with vasospasm and associated with unfavorable outcome at discharge. These patients were compared to those that made a complete recovery prior to discharge. However, microparticle levels were not associated with outcomes at 6-months. This is the only study that has investigated microparticles and outcome in SAH.

Vascular endothelial growth factor and anti-angiogenic factors—Vascular endothelial growth factor (VEGF) stimulates endothelial cell proliferation and permeability, increases intercellular adhesion molecule expression and leukocyte infiltration, and facilitates vascular smooth muscle cell migration and intimal proliferation (Carmeliet & Collen, 1998; Grosskreutz et al., 1999; McGirt et al., 2002; Melder et al., 1996). Therefore, it may play a key role in several signaling cascades related to injury in SAH. The increase in blood VEGF levels occur several days prior to the onset of vasospasm and neurological deterioration, and are strongly associated with the severity of the initial insult, clinical status upon admission, and the volume of SAH (McGirt et al., 2002). The specificity of VEGF for a particular damaging process has yet to be determined, but it may be an important early indicator of injury progression. VEGF and other vascular mitogens are regulated by circulating antiangiogenic factors, soluble-*fms*-like tyrosine kinase 1 (sFlt1) (Olsson et al., 2006) and soluble endoglin (sEng) (Bernabeu et al., 2007), and changing levels of these factors may be associated with outcome in SAH. Testai et al. (2011) recently examined levels of sFlt1 and sEng in a cohort of SAH patients and found an early increase, particularly in patients who developed focal neurological signs and/or deterioration in consciousness. In the same way that VEGF is involved in a host of cellular cascades, antiangiogenic factors may be involved in the modulation of a variety pathways leading to damage in SAH. The specificity of VEGF may be an important early indicator of injury progression and monitoring levels on a regular basis may be advantageous.

Complement cascade—The complement cascade, involved in erythrocyte hemolysis and activation of inflammation, may be involved in the pathogenesis of SAH-induced injury. Studies have demonstrated that upregulation of C3a, C4a and the membrane attack complex takes place after SAH (Kasuya & Shimizu, 1989; Lindsberg et al., 1996; Mack et al., 2007; Ostergaard et al., 1987). Mack et al. (2007) found that early C3a and C5a levels were significantly increased in SAH patients and were independent of clinical status upon admission. Early C3a levels strongly correlated with outcome and may be a useful serum biomarker for early inflammatory mediated damage after SAH.

von Willebrand factor—von Willebrand factor (vWF) is a large adhesive glycoprotein that is stored in endothelial cell Weibel-Palade bodies. Its specific cell source makes it a suitable serum biomarker of endothelial cell activation in SAH. Frijns et al. (2002, 2006a,b) found that SAH patients with vWF greater than or equal to the median value had an increased risk of poor outcome, with no increased risk for ischemia. In contrast, McGirt et al. (2002) found that vWF levels could accurately predict the occurrence of vasospasm. These preliminary studies demonstrate that vWF may be a useful marker for severity of injury and prognosis of clinical course in SAH.

Fibrinogen degradation products and thrombin-antithrombin (TAT) complex—Fibrinolytic agents may be administered after SAH to aid in clot removal. Anti-fibrinolytic therapy is known to increase the risk of vasospasm (Kassell et al., 1984). Patients with vasospasm have been shown to have lower blood levels of fibrinolytic activity (including D-dimer and TAT complexes) (Morga et al., 2007; Suzuki et al., 1997), increased fibrinogen (Frontera et al., 2012) and smaller hematoma load (Morga et al., 2007; Suzuki et al., 1997),

which has been associated with worsening clinical status (Frontera et al., 2012; Morga, et al., 2007. Morga et al. (2007) demonstrated that D-dimer and TAT complex formation were related to the clinical status of patients after SAH. They found that D-dimer and TAT levels were associated with hematoma volume and worsening of clinical status. Given these findings, D-dimer, fibrinogen and TAT serum levels may be useful biomarkers for worsening clinical course after SAH.

Cardiac markers

Cardiac abnormalities, including dysrhythmias and left ventricular systolic dysfunction, are a well-recognized phenomenon after SAH. The pathophysiology and contribution of cardiac dysfunction to outcome after SAH is controversial and is usually reversible. The most likely mechanism is excessive catecholamine release. Over the past 5 years, there have been a number of studies, in humans, that demonstrate a significant association between increased cardiac troponin I (cTnI) levels and morbidity and mortality in patients with SAH (Kumar et al., 2011; Miketic et al., 2010; Naidech et al., 2005; Ramappa et al., 2008; Sandhu et al., 2008; Schuiling et al., 2005; Yarlagadda et al., 2006). This neurologically mediated cardiac dysfunction is an independent predictor of mortality (Kumar et al., 2011; Miketic et al., 2010; Naidech et al., 2005; Ramappa et al., 2008; Sandhu et al., 2008; Schuiling et al., 2005; Yarlagadda et al., 2006). It is associated with severity of initial neurological injury including lower admission Glasgow coma scale, increased hospital stay, poor neurologic outcome (Ramappa et al., 2008) including functional recovery and disability (Miketic et al., 2010) and increased in-hospital morbidity and mortality (Kumar et al., 2011; Miketic et al., 2010; Naidech et al., 2005; Ramappa et al., 2008; Sandhu et al., 2008; Schuiling et al., 2005; Yarlagadda et al., 2006) after SAH. In recent years, cardiac dysfunction in patients after SAH have been associated with increased levels of blood B-type natriuretic peptide (BNP) as well (Taub et al., 2011). SAH patients with associated cardiac dysfunction present a unique challenge with regards to medical management. As mentioned in the introduction, complications of medical management can be quite devastating in these patients, in particular. Utilizing cTnI levels may assist in identifying those at risk for cardiopulmonary dysfunction as well as high-risk patients that may require modifications to therapy.

Other markers

There are other biomarkers that have been associated with outcome in SAH patients that are not categorized in any of the groups denoted above. They include malondialdehyde (MDA), kallikrein-6 (KLK6) and creatine kinase–BB (CK-BB). They each have a single study that demonstrates their association with poor outcome in SAH patients. MDA is a byproduct of lipid peroxidation and arachidonic acid metabolism and frequently used as an indicator of oxidative stress. Kaneda et al. (2010) demonstrated elevated MDA levels at Day 14 were associated with poor outcome. KLK6 is a serine protease enzyme whose physiological function is unknown. Nevertheless, Martinez-Morillo et al. (2012) demonstrated that decreased blood levels of KLK6 were associated with increased mortality. CK-BB is a creatine kinase found in the brain and is involved in energy maintenance within mitochondria. Coplin et al. (1999) demonstrated that increased CSF levels of CK-BB, greater than 40 U/L, was associated with unfavorable outcome at 1 week and 2 months after SAH.

Microdialysis

Intracerebral microdialysis is a technique used for sampling the extracellular molecular chemistry within brain tissue. Although the volume of brain tissue being analyzed is limited, it has been utilized in neurocritical care to monitor markers of ischemia and cell damage (Ungerstedt & Rostami, 2004). The most commonly utilized marker of microdialysis is the lactate/pyruvate ratio. However, other excitatory amino acids, such as glycerol and nitrate, have also been investigated. The lactate/pyruvate ratio is a marker of changes in the reduction and oxidation states associated with ischemia. Increased lactate/pyruvate ratios, excitatory amino acids and nitrate have been correlated to poor outcomes and neurological deterioration (Nilsson et al., 1999; Sarrafzadeh et al., 2003; Staub et al., 2000). Microdialysis has been used for the early detection of secondary insults after brain injury, such as SAH. Although there is great theoretical promise in monitoring molecular changes and metabolic disturbances associated with secondary insults early after brain injury, the quality of information gained from microdialysis will have to be exceptional to justify its added risk. Nevertheless, microdialysis demonstrates promise in regards to monitoring molecular changes and metabolic disturbances associated with secondary insults early after brain injury.

Conclusion

Subarachnoid hemorrhage is a devastating condition, whose progression, fatality and secondary debilitating outcome is the basis for ongoing research towards improving clinical management. Current standards of incorporating age, admission neurologic grade and admission CT scan assess the state of the patient on admission. Utilizing a prognostic serum biomarker, with continuous daily evaluation and ability to monitor trends, would allow patients to be monitored during the acute phase and assist in the management and treatment of SAH patients. These biomarkers would identify those that necessitate more aggressive management, those that may warrant closer monitoring, promote early treatment models and predict long-term outcome. The elevation in certain biomarkers may be detected prior to the presentation of neurological deterioration. Therefore, patients may be identified earlier, in the acute period, as high risk for poor outcome. These patients may require a prolonged duration of a higher level of care (i.e. intensive critical care) including frequent neurological examinations and continuous monitoring. Currently, some SAH patients are transferred to a lower level of care based on their neurological examinations and progress, only to return to the intensive care unit after neurological deterioration. Management for these “high-risk” patients, once identified, may include initiation of increased systolic blood pressure and mean arterial pressure goals as well as increased fluid resuscitation (early initiation of “triple H” therapy). This preemptive management may decrease the risk of deterioration in some of these patients and may ultimately improve their outcome. This may also decrease the number of emergent imaging studies that are initiated after acute neurological deterioration, as it may prevent some of these patients from deteriorating; therefore, enhance the feasibility of biomarker monitoring. However, due to the lack of evidence and excellent sensitivities and specificities of any single biomarker, their utilization in the standard of care in the acute phase of SAH has not been accepted. Further research to identify specific biokinetics of these biomarkers, including appropriate ranges, specific peaks and half-lives, must be done

to improve their sensitivities and specificities and their translation into clinical medicine. Currently, prognostic biomarkers after SAH include neuronal-specific markers, inflammatory markers, molecular adhesion and matrix markers, vascular and angiogenic markers, coagulation function, cardiac markers and molecules of microdialysis.

This review details biomarkers that potentially, used in combination with current imaging and neurological examinations, may innately have the ability to predict and monitor high-risk patients and may improve outcome. Focusing specifically on blood biomarkers, secondary to the ease of access and sampling, in the acute period after SAH, S100β, CRP, adhesion and matrix markers, vasogenic markers and cardiac markers (TnI) demonstrate promise. Each of them have been demonstrated to correlate with outcome; however, their sensitivities and specificities must be improved before translation and utilization. Further research in the development and implementation of serum biomarkers of outcome in SAH would establish a safe, more cost effective standard monitoring tool that would allocate resources more efficiently, improve clinical management and may decrease morbidity and mortality.

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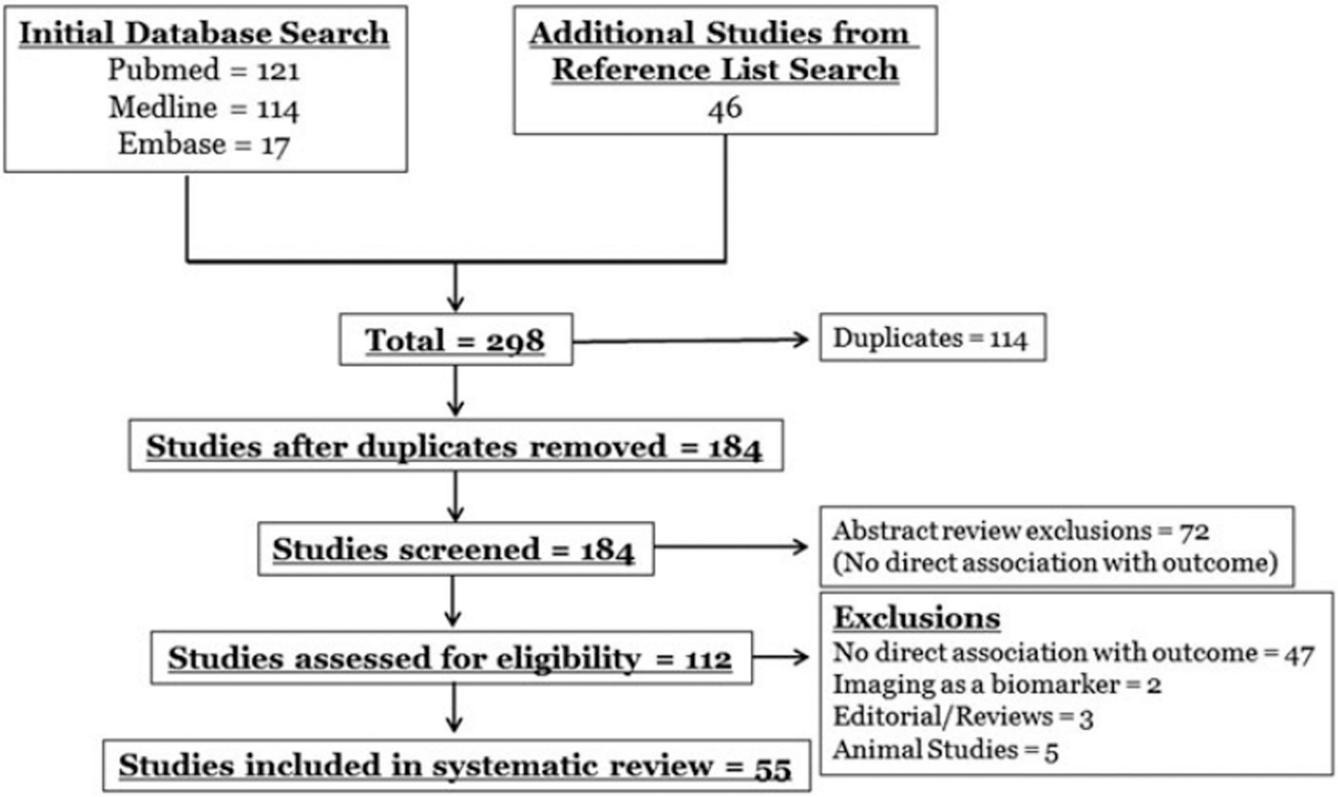

Figure 1.
Search results.

Table 1

Summary of studies reporting biomarkers associated with outcome in SAH.

Biomarker	#of patients	Detection substrate	Summary of findings and outcome scale used	Author, year
Neuron and astrocyte-specific markers				
S100β	32	CSF	Univariate analysis demonstrated increased S100β associated with poor outcome (GOS)	Kaneda et al., 2010
	109	Blood	S100β is excellent predictor of 12-month outcome (GOS)	Sanchez-Pena et al., 2008
	55	CSF/Blood	Increased CSF and blood S100β was associated with outcome prognosis (GOS)	Moritz et al., 2010
	52	Blood	S100β indicator of scale and severity as well as prognostic indicator of 1 year outcome. (GOS)	Stranjalis et al., 2007
	74	Blood	Level of S100β correlated with initial SAH severity and at day 8 was an independent predictive factor for outcome at 6 months (GOS)	Weiss et al., 2006
	51	Blood	Elevated S100β associated with increased mortality and unfavorable outcome at 6 months (GOS)	Oertel et al., 2006
	67	Blood	Elevations of S100β was associated with poor outcome (GOSE)	Vos et al., 2006
	43	Blood	Mean values of S100β predictor of outcome (GOS)	Schick et al., 2003
	71	Blood	Elevations of S100β correlate with early neurological deficits (7 days) and worse outcome at 6 months (GOS)	Wiesmann et al., 1997
	45	CSF	Increased S100β associated with severity of injury, clinical course, delayed ischemic deterioration and outcome (GOS)	Hardemark et al., 1989
Neuron-specific enolase (NSE)-conflicting	55	CSF	Increased CSF levels of NSE associated with poor outcome at discharge from ICU (GOS)	Moritz et al., 2010
	29	Blood	Increased NSE levels associated with poor outcome at discharge (GOS)	Mabe et al., 1991
Glial fibrillary acid protein (GFAP)	32	CSF	Univariate analysis demonstrated increased GFAP associated with poor outcome (GOS)	Kaneda et al., 2010
	116	Blood	GFAP independent predictor of outcome after 1 year (GOSE)	Nylen et al., 2007
	67	Blood	Elevations of GFAP associated with poor outcome (GOSE)	Vos et al., 2006
Apolipoprotein E (ApoE)	47	CSF	Decreases correlated with poor clinical outcome at 3 months (GOS)	Kay et al., 2003a,b
APOE gene	46	Genotyping	E4 carriers trend towards detrimental long term effect on cognitive function (10 year longitudinal study)	Louko et al., 2006
	101	Genotyping	E4 expression prognostic for clinical VSP and higher risk of definitive neurologic deficits at least 6 months (MMSE and RDI)	Lanterna et al., 2005
	108	Genotyping	E4 gene expression prognostic factor for poor outcome with a risk of unfavorable outcome 7.1 times higher noncarriers (GOS)	Niskakangas et al., 2001
	227	Genotyping	E4 association with unfavorable outcome at 3 months (GOS)	Tang et al., 2003

Biomarker	#of patients	Detection substrate	Summary of findings and outcome scale used	Author, year
	72	Genotyping	E4 carriers associated with poor outcome at 6 months (GOS)	Leung et al., 2002
Neurofilament	30	CSF	Phosphorylated neurofilament subunit (pNF-H) elevations from the second week predict poorer outcome (GOSE)	Lewis et al., 2010
	148	CSF	Neurofilament heavy chain elevations in CSF associated with bad outcome at 3 months (GOS)	Petzold et al., 2006
	48	CSF	Neurofilament protein elevation in CSF correlates with neurological status in-hospital and 1-year outcome (GOSE)	Nylen et al., 2006
Amyloid B-protein	47	CSF	Decreases levels correlated with poor clinical outcome at 3 months (GOS)	Kay et al., 2003a,b
Ubiquitin C terminal Hydrolase 1 (UCHL1)	30	CSF	Elevation from the second week predict poorer outcome (GOSE)	Lewis et al., 2010
Inflammatory markers				
CRP	116	Blood	Early elevations of CRP prognostic for poor outcome (mRS)	Jeon et al., 2012
	178	Blood	Elevated CRP predict risk for poor outcome (GOS)	Juvela, 2000
	25	Blood	Elevated CRP associated with worse admission grade and poor GCS and NIHSS scores	Frontera et al., 2012
	82	Blood	Inverse relationship between CRP and GOS at discharge (GOS and mRS)	Romero et al., 2012
	110	Blood	hsCRP in patients who had delayed cerebral ischemia and poorer outcome at 3 months (mRS)	Badjatia et al., 2011
	41	Blood	CRP levels were inversely related to GOS and mRS scores on discharge	Fountas et al., 2009
	33	Blood	Increased levels of CRP were associated with delayed ischemic neurologic deficit at day 0 and day 7 after SAH	Kubo et al., 2008
TNF-α	52	Blood	Elevations of TNF-α on Day 2 to 3 is significantly associated with poor at 3-month with a similar trend at 6 months (mRS)	Chou et al., 2012
	52	CSF	Increased TNF-α associated with unfavorable outcome at 3 months (GOS)	Nakahara et al., 2009
	22	CSF	Increased TNF-α associated with unfavorable outcome at 12 days post SAH (GOS)	Mathiesen et al., 1997
IL-1	22	CSF	Increased IL-1Ra (IL-1 receptor antagonist) associated with unfavorable outcome at 12 days post SAH (GOS)	Mathiesen et al., 1997
IL-6	52	CSF	Increased IL-6 associated with unfavorable outcome at 3 months (GOS)	Nakahara et al., 2009
	35	CSF/Blood	Increased IL-6 in CSF significantly increased in patients with poor clinical outcome (Day 11) (GOS)	Fassbender et al., 2001
IL-8	52	CSF	Increased IL-8 associated with unfavorable outcome at 3 months (GOS)	Nakahara et al., 2009
High-mobility Group Box 1 protein (HMGB1)	52	CSF	Increased HMGB1 associated with unfavorable outcome at 3 months (GOS)	Nakahara et al., 2009

Biomarker	#of patients	Detection substrate	Summary of findings and outcome scale used	Author, year
Catecholamine	102	CSF	Elevated CSF epinephrine independent predictor of mortality and disability at 30 days	Moussouttas et al., 2012
	21	CSF/Blood	Elevated CSF epinephrine and norepinephrine associated with patients with focal ischemic deficits	Dilraj et al., 1992
Microalbuminuria	51	Urine	High microablumin/creatinine ration (MACR), >200 mg/g, in first 8 days from SAH predictor of unfavorable neurological outcome at 3 months (GOS)	Terao et al., 2007
Molecular adhesion and extracellular matrix markers				
MMP-9	55	CSF/Blood	Elevation of MMP-9 associated with poor 3-month clinical outcome (mRS)	Chou et al., 2011
ICAM-1, VCAM-1	33	Blood	Increased levels of ICAM-1 and VCAM-1 were associated with delayed ischemic neurologic deficit at day 0 and day 7 after SAH	Kubo et al., 2008
	78	CSF/Blood	Very high CSF ICAM-1 and VCAM-1 associated with unfavorable outcome and/or symptomatic VSP (GOS at discharge)	Kaynar et al., 2004
	158	Blood	ICAM-1 associated with patients with SAH with poor outcome at day 14 (mRS)	Mack et al., 2002
Selectin	21	Blood	sL-selectin associated with poor outcome at 6 months (BI)	Wang et al., 2011
Vascular and angiogenic markers				
Endothelial microparticles	20	Blood	MP higher at discharge but no significant differences after 6 months (mRS and GOS)	Lackner et al., 2010
VEGF	38	Blood	Increased levels of VEGF predict onset of delayed VSP before onset or neurological deterioration	Mcgirt et al., 2002
Caspase-3	52	Blood	Regression analysis demonstrated early C3a strong independent predictor of functional outcome	Mack et al., 2007
Coagulation factor markers		Blood		
vWF	90	Blood	Early levels of vWF associated with delayed cerebral ischemia and poor outcome at 12–14 weeks (mTS)	Frinjs et al., 2006a,b
Fibrinogen	25	Blood	Elevated fibrinogen correlated with worse Barthel scores at 14 days and trended to worse Barthel index at 3 months (BI)	Frontera et al., 2012
	72	Blood	Elevated levels strongly correlated with mortality	Morga et al., 2007
Thrombin-antithrombin complex (TAT)	72	Blood	Elevated levels strongly correlated with mortality	Morga et al., 2007
Cardiac markers				
Cardiac troponin I (cTnI)	41	Blood	Neurologic outcome during hospital stay was adversely related to increased cTnI and wall motion abnormalities, predicting poor GCS on admission and increased hospital stay (GOS)	Kumar et al., 2011
	239	Blood	Patients with elevated cTnI more severe aSAH symptoms and levels ≥0.3 ng/ml independent predictor of poor functional outcome at 2 months (GOS and mRS)	Miketic et al., 2010

Biomarker	#of patients	Detection substrate	Summary of findings and outcome scale used	Author, year
	378	Blood	In-hospital mortality significantly increased with increased TnI	Sandhu et al., 2008
	83	Blood	Elevated cTnI predictor of in-hospital mortality	Ramappa et al., 2008
	300	Blood	Strong association between TnI and in-patient mortality	Yarlagadda et al., 2006
	68	Blood	cTnI elevations independent prognostic indicator of poor outcome at 3 months (mRS)	Schuiling et al., 2005
Other markers				
Malondialdehyde (MDA)	32	CSF	At 2 weeks, elevations of MDA predictor of poor neurological outcome at 6 months (GOS)	Kaneda et al., 2010
Kallikrein-related peptidase-6 (KLK6)	13	Blood	Kallikrein-related peptidase 6 (KLK6) was significantly lower in patients with severe disability or death.	Martinez-Morillo et al., 2012
Creatine Kinase-BB (CK-BB)	30	CSF	Increased levels of CK-BB > greater than 40 U/L were associated with unfavorable outcome at 1 week and 2 months (GOS)	Coplin et al., 1999
Microdialysis (MD)				
Lactate	95	Brain tissue	Significantly higher in patients with acute focal neurological deficits and correlated with neurological worsening at 6 and 12 months (GOS)	Sarrafzadeh et al., 2003
	10	Brain tissue	Elevations significantly correlated with poor outcome at 3 months (GOS)	Staub et al., 2000
Pyruvate	95	Brain tissue	Decreased levels in patients with acute focal neurological deficits and correlated with neurological worsening at 6 and 12 months (GOS)	Sarrafzadeh et al., 2003
Excitatory amino acids (EAA)	95	Brain tissue	Significantly higher in patients with acute focal neurological deficits and correlated with neurological worsening at 6 and 12 months (GOS)	Sarrafzadeh et al., 2003
	10	Brain tissue	Elevations significantly correlated with poor outcome at 3 months (GOS)	Staub et al., 2000
Nitrate	10	Brain tissue	Elevations significantly correlated with poor outcome at 3 months (GOS)	Staub et al., 2000

GOS: Glasgow Outcome Scale; GOSE: Glasgow Outcome Scale Extended; MMSE: Mini-Mental State Examination; RDI: Rankin Disability Index; mRS: Modified Rankin Score; mTS: Modified Tardieu Scale; BI: Barthel Index.