S100B Serum Elevation Predicts In-Hospital Mortality After Brain Arteriovenous Malformation Rupture

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Brief Report

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Background and Purpose—S100B protein serum elevation has been associated with poor prognosis in neurologically ill patients. The purpose of this study is to determine whether elevation of S100B is associated with increased in-hospital mortality after brain arteriovenous malformation rupture.

Methods—This is a retrospective study of patients admitted for brain arteriovenous malformation rupture. The study population was divided into derivation and validation cohorts. Univariate followed by multivariate logistic regression was used to determine whether elevation of S100B serum levels above 0.5 µg/L during the first 48 hours after admission (S100Bmax48) was associated with in-hospital mortality.

Results—Two hundred and three ruptures met inclusion criteria. Twenty-three led to in-hospital mortality (11%). Mean S100Bmax48 was 0.49±0.62 µg/L. In the derivation cohort (n=101 ruptures), multivariate analysis found Glasgow coma scale score ≤8 (odds ratio, 21; 95% CI, 2–216; 0.001) and an S100Bmax48>0.5 µg/L (odds ratio, 19; 95% CI, 2–188; *P*=0.001) to be associated with in-hospital mortality. When applied to the validation cohort (n=102 ruptures), the same model found only S100Bmax48>0.5 µg/L (odds ratio, 8; 95% CI, 1.5–44; *P*=0.01) to be associated with in-hospital mortality.

Conclusions—Elevated S100B protein serum level is strongly associated with in-hospital mortality after brain arteriovenous malformation rupture. **(*Stroke*. 2019;50:00-00. DOI: 10.1161/STROKEAHA.119.025033.)**

Key Words: arteriovenous malformation ■ brain ■ intracranial hemorrhage ■ mortality ■ prognosis

Brain arteriovenous malformation (BAVM) rupture is the leading cause of morbidity and mortality in this disease. Predicting outcome after BAVM rupture has mainly relied on demographic, clinical, and imaging markers.[1] S100B serum level elevation has been found to be associated with severity of neurological insult in neurocritically ill patients.[2] The present study aimed to determine whether elevation of S100B is associated with in-hospital mortality after BAVM rupture.

Methods

Data Availability

Study data are available from the corresponding author on reasonable request.

Patients

Records of patients with BAVM ruptures admitted between January 1, 2003, and December 1, 2018, were retrospectively reviewed. Hemorrhages within 7 days of a partial embolization were excluded. All patients were admitted within 24 hours of hemorrhage. One hundred thirteen ruptures included in this study were previously included in a report of long-term outcome after BAVM rupture.[1]

Ethical Statement

The ethics committee of our institution approved this study. The need for patients' informed consent was waived.

S100B Protein Serum Level

Admission S100B serum level and subsequent sampling within the following 48 hours were retrospectively recorded. In most patients, samples were drawn on admission and daily afterwards. Admission samples were unavailable for a minority of patients, and some patients had several samples drawn on the same day (because of acute deterioration for instance). Clinicians were aware of S100B levels in real time. Since December 2, 2010, S100B has been assayed on ModularE170 analyzer (Roche, Mannheim, Germany). Results assessed before that date were measured on a LiaisonXL (Diasorin, Saluggia, Italy); therefore, these values were corrected as ([concentration]–0.01)/2.28, according to the linear regression between the 2

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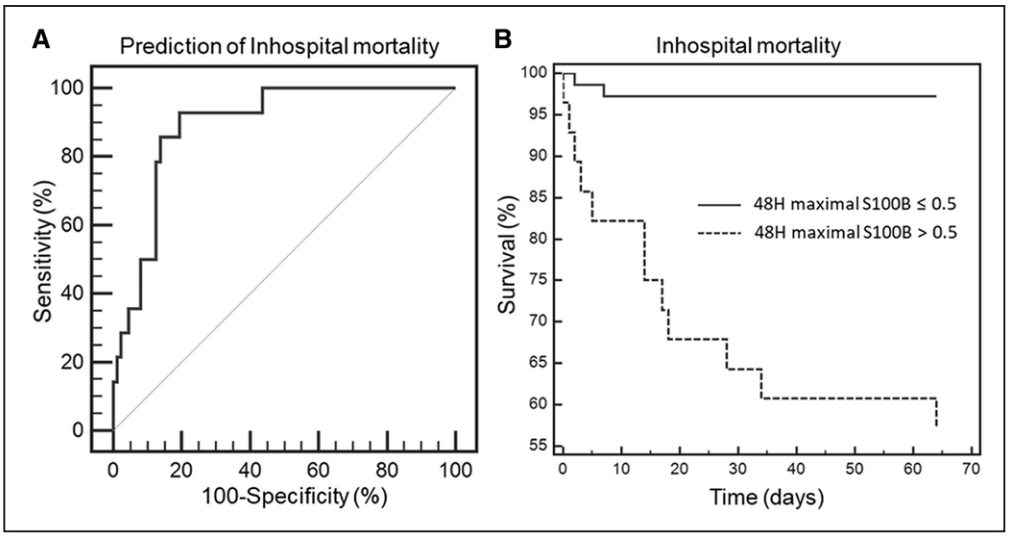

Figure. In-hospital mortality. **A**, Receiver operating characteristic (ROC) curve for S100B maximal serum levels within 48 h after admission (S100Bmax48) and in-hospital mortality in the derivation cohort. **B**, Kaplan-Meier survival curve comparing patients with an S100Bmax48>0.5 µg/L and ≤0.5 µg/L in the derivation cohort.

methods.[3] The highest S100B value during the first 48 hours after admission (S100Bmax48) was used for subsequent analysis.

End Points

The primary end point was in-hospital mortality. Secondary end point was poor neurological outcome (mRS score ≥3 more than 3 months after admission).

Statistical Analysis

The study population was randomly subdivided into derivation and validation cohorts. The following analysis was performed on the derivation cohort: Receiver operating characteristic curve for S100Bmax48 and in-hospital mortality was drawn, an optimal S100Bmax48 threshold was chosen based on the receiver operating characteristic curve, and Kaplan-Meier survival analysis was performed. To identify factors independently associated with in-hospital mortality, univariate followed by bidirectional stepwise multivariate logistic regressions was performed on data from the derivation cohort. A variable was included in the multivariate model if it was associated with $P<0.05$ in univariate analysis. At each step of the stepwise logistic regression, variables with $P>0.1$ were dropped. The same multivariate regression model was tested on the validation cohort. Sensitivity analysis is described in Material in the online-only Data Supplement.

Binary variables are expressed as percentages (with 95% CIs) and continuous variables as mean±SD. All tests were 2-sided. P values <0.05 were considered significant. Statistical analyses were performed using MedCalc version 11.3.0.0 (Ostend, Belgium).

Results

During the study period, 252 BAVM ruptures were identified. One hundred ninety-eight patients presenting with 203 independent hemorrhagic events met inclusion criteria (flow chart, Figure I in the online-only Data Supplement). Table I in the online-only Data Supplement shows patients' characteristics in the entire population. Twenty-three hemorrhages led to in-hospital mortality (11%). Mean and median elapsed time between admission and death was 17 days (range, 0–64 days). In the entire study population, mean admission S100B concentration (available for 178/203 ruptures) was 0.45±0.57 µg/L. Mean S100Bmax48 was 0.49±0.62 µg/L.

In the derivation cohort (101 ruptures), the area under the receiver operating characteristic curve for S100Bmax48 values as a predictive factor of in-hospital mortality was 0.89 (Figure 1A). The optimal S100Bmax48 threshold according to receiver operating characteristic curve analysis was 0.46 µg/L, with a sensitivity and specificity of 92% and 80%, respectively. A 0.5 µg/L cutoff was chosen as an approximation of the optimal threshold. Survival analysis demonstrated a significantly higher rate of in-hospital mortality in patients with an S100Bmax48>0.5 µg/L (hazard ratio, 19; 95% CI, 6–65; $P<0.0001$; Figure 1B).

To determine whether S100B elevation was independently associated with in-hospital mortality, univariate followed by multivariate logistic regression was performed in the derivation cohort (Table). Only 2 factors were found to be independently and significantly associated with in-hospital mortality: Glasgow Coma Scale score ≤8 (odds ratio [OR], 21; 95% CI, 2–216; $P=0.001$) and an S100Bmax48>0.5 µg/L (OR, 19; 95% CI, 2–188; $P=0.001$). When applied to the validation cohort (102 ruptures), the same model demonstrated only S100Bmax48>0.5 µg/L to be associated with in-hospital mortality (OR, 8; 95% CI, 1.5–44; $P=0.01$).

Sensitivity analysis showed the effect of S100Bmax48 elevation on in-hospital mortality on the entire population was stable both in direction and magnitude, with thresholds between 0.3 and 1.5 µg/L (Table II in the online-only Data Supplement). The initial S100B samples (within the first 24 and 48 hours after admission), with a 0.5 µg/L threshold, were also shown to be associated with in-hospital mortality. Finally, when the model was applied to prediction of poor neurological outcome, S100Bmax48>0.5 µg/L was found to be an independent predictive variable (OR, 5; 95% CI, 2–12; $P<0.001$) along with Glasgow Coma Scale score ≤8 (OR, 6; 95% CI, 2–17; $P<0.001$).

The sensitivity and specificity of S100Bmax48>0.5 µg/L for predicting in-hospital mortality was compared with those of imaging markers generally associated with poor outcome in the complete study population. For S100Bmax48>0.5 µg/L,

Table. Logistic Regression Analysis for Association With In-Hospital Mortality in the Derivation Cohort

	In-Hospital Mortality (14/101 BAVM Ruptures)	In-Hospital Survival (87/101 BAVM Ruptures)	Predictive Factors of Inpatient Mortality			
			Univariate Analysis		Multivariate Stepwise Logistic Regression	
			OR [95% CI]	*P* Value	OR [95% CI]	*P* Value
Demographics and medical history						
Age	44±16	45±15	1 [0.95–1.03]	0.81		
Male	9/14 (64)	47/87 (54)	0.7 [0.2–2]	0.47		
History of high BP	1/14 (7)	18/87 (21)	0.3 [0.04–2]	0.25		
Past BAVM rupture	4/14 (29)	10/87 (11)	3 [0.8–12]	0.1		
Admission characteristics						
GCS ≤8	11/13 (85)	14/87 (16)	29 [6–144]	<0.0001*	21 [2–216]	0.001
Heart rate	75±21	75±15	1 [0.96–1.04]	0.99		
Mean blood pressure	97±15	98±18	1 [0.96–1.03]	0.87		
Hemorrhage characteristics						
Infratentorial ICH	2/14 (14)	14/87 (16)	0.9 [0.2–4]	0.85		
ICH ≥30 mL	9/14 (64)	35/84 (42)	3 [0.8–8]	0.12		
ICH ≥60 mL	8/17 (64)	19/84 (23)	5 [1.4–15]	0.01*		
IVH	14/14 (100)	52/86 (60)	NA	0.0004*		
SAH	5/14 (36)	22/86 (26)	2 [0.5–5]	0.43		
SDH	0/14 (0)	9/86 (10)	NA	0.99		
Biological parameters						
S100Bmax48>0.5 µg/L	12/14 (86)	16/87 (18)	27 [5–131]	0.0001*	19 [2–188]	0.001
Plasma troponin elevation	5/13 (38)	6/67 (9)	6 [2–26]	0.01*		
Serum creatinine, µmol/L	65±34	62±15	1 [0.98–1.04]	0.61		

Values are mean±SD for quantitative variables or percentage for qualitative variables. BAVM indicates brain arteriovenous malformation; BP, blood pressure; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; OR, odds ratio; SAH, subarachnoid hemorrhage; and SDH, subdural hemorrhage.

*Variable included in the multivariate regression model.

sensitivity and specificity were 78% and 79%, respectively. For intracerebral hemorrhage (ICH) volume ≥60 mL, sensitivity and specificity were 48% and 78%, respectively. For infratentorial ICH, sensitivity and specificity were 26% and 86%, respectively. For intraventricular hemorrhage, sensitivity and specificity were 96% and 38%, respectively.

Discussion

In-hospital mortality in this cohort of BAVM ruptures was 11%. S100B protein serum elevation above 0.5 µg/L during the first 48 hours after admission was independently and significantly associated with in-hospital mortality.

Prognostic markers provide a basis for decision-making regarding the most appropriate level of care in neurocritically ill patients.[1] Prognosis is a major thematic domain of questioning by relatives of intensive care unit patients.[4] Providing relatives with high-quality prognostic information enhances their ability to actively participate in the decision-making process regarding aggressive therapeutic interventions.[4] The ICH Hemphill score provides prognostic stratification for patients with primary and secondary ICH.[5] ICH, ICH volume, intraventricular hemorrhage, and Glasgow Coma Scale have been associated with outcome in BAVM rupture.[1,6] In this retrospective cohort, S100B elevation appears to be a stronger prognostic marker than any of the imaging markers studied. S100Bmax48>0.5 µg/L demonstrated higher sensitivity and specificity than an ICH volume ≥60 mL in predicting in-hospital mortality. The presence of an infratentorial ICH had higher specificity but with a collapsed sensitivity, and the reverse was found to be true for the presence of an intraventricular hemorrhage.

Special care should be taken when handling early prognostic markers of poor outcome in clinical practice as overconfidence can lead to self-fulfilling prophecy. This consideration is particularly relevant in neurocritically ill patients who often die when life-sustaining treatment is withheld or withdrawn.[7] Nevertheless, it has been argued that to limit self-fulfilling prophecy, it is critical to collect and appraise more evidence, rather than less, about prognosis and prognostic markers.[7] Beyond prognostication, biomarkers can be used for follow-up during intensive care stay. This is useful in neurocritically ill patients, often comatose or sedated, in which neurological examination often fails to diagnose late complications such as rebleeding, vasospasm, or hydrocephalus. Given the results of this study, we recommend sampling S100B protein

on admission of patients with BAVM rupture as a prognostic marker and serving as baseline for subsequent follow-up.

The monocentric retrospective design of this study conducted in a tertiary care center may limit external validity. Clinicians were aware of S100B protein levels in real time, leading to a risk of self-fulfilling prophecy. Moreover, it would be difficult to validate these findings in an external cohort as S100B is not routinely measured in many institutions. Only S100B was measured in this population and could not be compared with other markers. S100Bmax48 was the main prognostic marker tested in this study because of previous reports demonstrating delayed S100B serum elevation having a stronger association with outcome after traumatic injury, potentially reflecting the impact of secondary neurological injuries.[8] It is noteworthy, however, that sensitivity analysis demonstrated that S100B sampling at other time points was also predictive of mortality.

Summary

Elevated S100B was predictive of in-hospital mortality after BAVM rupture in this single-center retrospective cohort.

Disclosures

None.

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