Inflammation, negative nitrogen balance, and outcome after aneurysmal subarachnoid hemorrhage

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ABSTRACT

Objective: To analyze the impact of inflammation and negative nitrogen balance (NBAL) on nutritional status and outcomes after subarachnoid hemorrhage (SAH).

Methods: This was a prospective observational study of SAH patients admitted between May 2008 and June 2012. Measurements of C-reactive protein (CRP), transthyretin (TTR), resting energy expenditure (REE), and NBAL (g/day) were performed over 4 preset time periods during the first 14 postbleed days (PBD) in addition to daily caloric intake. Factors associated with REE and NBAL were analyzed with multivariable linear regression. Hospital-acquired infections (HAI) were tracked daily for time-to-event analyses. Poor outcome at 3 months was defined as a modified Rankin Scale score ≥4 and assessed by multivariable logistic regression.

Results: There were 229 patients with an average age of 55 ± 15 years. Higher REE was associated with younger age ($p = 0.02$), male sex ($p < 0.001$), higher Hunt Hess grade ($p = 0.001$), and higher modified Fisher score ($p = 0.01$). Negative NBAL was associated with lower caloric intake ($p < 0.001$), higher body mass index ($p < 0.001$), aneurysm clipping ($p = 0.03$), and higher CRP:TTR ratio ($p = 0.03$). HAIs developed in 53 (23%) patients on mean PBD 8 ± 3. Older age ($p = 0.002$), higher Hunt Hess ($p < 0.001$), lower caloric intake ($p = 0.001$), and negative NBAL ($p = 0.04$) predicted time to first HAI. Poor outcome at 3 months was associated with higher Hunt Hess grade ($p < 0.001$), older age ($p < 0.001$), negative NBAL ($p = 0.01$), HAI ($p = 0.03$), higher CRP:TTR ratio ($p = 0.04$), higher body mass index ($p = 0.03$), and delayed cerebral ischemia ($p = 0.04$).

Conclusions: Negative NBAL after SAH is influenced by inflammation and associated with an increased risk of HAI and poor outcome. Underfeeding and systemic inflammation are potential modifiable risk factors for negative NBAL and poor outcome after SAH. ***Neurology*®** **2015;84:680–687**

GLOSSARY

CRP = C-reactive protein; **DCI** = delayed cerebral ischemia; **HAI** = hospital-acquired infection; **ICU** = intensive care unit; **IDC** = indirect calorimetry; **mRS** = modified Rankin Scale; **NBAL** = nitrogen balance; **PBD** = postbleed day; **REE** = resting energy expenditure; **SAH** = subarachnoid hemorrhage; **SHOP** = SAH outcomes project; **TTR** = transthyretin; **UUN** = urine urea nitrogen.

Aneurysmal subarachnoid hemorrhage (SAH) is a significant contributor to all stroke-related potential years of life lost before age 65 years.[1] Much of this is attributed to delayed cerebral ischemia (DCI).[2] However, recent studies have found that both medical and infectious complications are significant independent contributors to morbidity and mortality after SAH.[3–5] We previously found an association between poor nutritional status and infectious complications acutely after SAH.[6]

Malnutrition has been associated with impaired immunologic function leading to increased rates of infection.[7] An assessment of nutritional profiles measured by indirect calorimetry (IDC) found SAH patients to have average resting energy expenditure (REE) rates between 40% and 75% above baseline levels,[8,9] with a possible association between an increased catabolic state and cerebrovascular vasospasm.[8]

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Supplemental data at Neurology.org

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The purpose of this study was to describe the relationship among inflammation, as measured by C-reactive protein (CRP) and transthyretin (TTR), nutritional status, and hospital-acquired infections (HAIs) in the first 2 weeks after SAH. We hypothesized that protein catabolism would be associated with markers of inflammation and HAIs after SAH.

METHODS

Patient selection and data collection. This is a prospective observational study of aneurysmal SAH patients admitted to the neuro–intensive care unit (ICU) at Columbia University Medical Center between April 2008 and June 2012. Clinical care for SAH patients has been described previously[10] and conformed to established guidelines.[1,11] All craniotomy patients were treated with IV steroids (dexamethasone 10 mg) intraoperatively and were continued on a scheduled taper for the first 5 postoperative days. Nutritional support was standardized to begin within 24 hours after aneurysmal repair with goals determined by energy expenditure estimates using a modification of the American College of Chest Physicians equation estREE = 25 × adjusted body weight (kg).[12] Adjustments in caloric goals were made for patients on propofol infusions. A clinical nutritionist determined the type of enteral formula used. All nutrition assessments were adjusted for admission body weight.

Study enrollment criteria were as follows. Inclusion criteria were (1) SAH due to a ruptured aneurysm detected by angiography; (2) age ≥18 years; and (3) admission ≤48 hours of hemorrhage. Exclusion criteria were (1) death from withdrawal of care or brain death expected within ≤72 hours of hemorrhage; (2) ICU length of stay expected to be ≤72 hours; (3) unable to perform IDC within 72 hours of hemorrhage due to patient refusal, agitation, or high FiO_2 requirement (≥0.6); and (4) inability to assess urine urea nitrogen levels due to inadequate urine output.

All subjects underwent serial assessments of inflammatory and metabolic parameters during the first 14 days after SAH. Each assessment was conducted once during 4 predefined time periods: postbleed day (PBD) 0–3, PBD 4–7, PBD 8–10, and PBD 11–14. All inflammatory and metabolic parameters were measured during the same 24-hour period within each period. Data collection was considered complete in instances when patients died or were discharged from the hospital prior to completion of the 4 periods.

SAH data collection. The data collection materials and practices used in the ongoing SAH outcomes project (SHOP) have been described previously.[2] All subjects were tested at discharge or PBD 14, whichever was sooner, and at 3 months for functional disability. Each subject was screened daily for the development of vasospasm and DCI using established criteria.[13,14]

Infectious complications. Each subject was screened daily for the development of infectious complications, using established criteria for HAIs.[15] We recorded the calendar date for each infectious complication, which allowed for the quantification of the true incidence of HAIs as those infections that developed ≥72 hours after ictus and for time to event analysis.[16]

Nutritional measurements. Oxygen consumption (VO_2), REE, urine urea nitrogen (UUN), serum TTR (a.k.a. prealbumin), and daily caloric intakes were linked to the comprehensive data collection from SHOP at the time of analysis.

IDC. Our methodology for IDC has been described previously.[17,18] In mechanically ventilated subjects, the IDC circuit system was connected to the oxygen delivery and exhaust systems of the ventilator, whereas in non–mechanically ventilated subjects, the IDC circuit was connected to an airtight canopy that covered the subject's head and neck and delivered a measured constant flow of air (21% O_2).

Caloric intake. Caloric intake was measured daily. For ventilated subjects, daily total caloric intake was assessed daily from oral and enteral nutrition, dextrose infusions, and sedatives (propofol). The conversion to calories for dextrose was 3.4 calories/g, and for propofol infusions was 1.1 calories/mL. All nutritional sources were further broken down into percentage of calories from fat, carbohydrate, and protein calculated by the clinical nutritionist staff at the Bionutrition Unit at the Columbia University Irving Institute for Clinical and Translational Research. For enteral nutrition, this was obtained from information packets for each type of enteral formula. In subjects able to take oral nutrition, neuro-ICU nurses and study staff were trained to evaluate and record daily caloric intake from each meal by clinical nutritionists. These food diaries, along with daily menus, were then tabulated to determine the total caloric intake as well as percentage of calories from protein, carbohydrate, and fat.

Outcome assessments. Global outcome was assessed prospectively at 14 days and 3 months posthemorrhage with a 7-point version of the modified Rankin Scale (mRS) rated from death to symptom-free full recovery.[19] Poor outcome was defined as a mRS score of ≥4. All clinical and outcome endpoints were classified according to a priori criteria and adjudicated at a weekly SHOP database meeting, which required a consensus agreement of each endpoint by neurocritical care faculty after a complete review of source documentation, imaging, and laboratory tests.

Statistical analysis. This study was planned for a 4-year enrollment, during which time it was estimated that there would be approximately 250 subjects meeting study criteria with approximately 26% developing HAIs.[3] This would allow for >90% power to demonstrate a statistically significant ($\alpha = 0.05$) difference in mean negative nitrogen balance of at least 2 g/day, assuming a SD of 4 g/day.

Continuous variables were assessed for normality and reported using accepted standards for parametric and nonparametric data. Categorical variables were reported as count and proportions in each group. The laboratory values for both TTR and CRP were reported in mg/dL. All nutritional and metabolic values were reported in terms of amount per day. In addition, caloric intake was reported in weight-adjusted values per day, utilizing the admission weight (kilograms).

Multivariable linear regression analyses were performed to determine factors associated with REE or nitrogen balance by entering in those factors found to have a p value ≤0.1 on univariate analysis. The occurrence of the first HAI was treated as a censored event by PBD and corresponding study period. Baseline characteristics that were found on univariate analysis to be associated ($p < 0.1$) with HAI were entered into a Cox proportional hazards model to calculate hazard ratios and corresponding 95% confidence intervals for developing HAI. Multivariate logistic regression was performed to determine factors associated with poor outcome 3 months after SAH. Tests for interaction were performed and reported when found to be significant. For all tests, significance was set at $p < 0.05$. All analyses were performed with SPSS v21.0 (Chicago, IL).

Standard protocol approvals, registrations, and patient consents. Consent and conduct of both studies was approved by the institutional review board and consistent with guiding principles for research involving humans.[20] Given the observational design and utilization of residual blood and urine for laboratory assessments, this study was conducted with a waiver of consent. Data were linked with the SHOP database, which utilized a tiered consent process, whereby consent was obtained from those patients who were able to provide consent at the time of injury. In neurologically impaired patients, family members were approached for participation in the study and if capacity was regained, patients were directly approached for consent.

RESULTS **Baseline characteristics.** There were 285 SAH patients admitted with 229 meeting study criteria. The reasons and number of patients excluded are shown in figure e-1 on the *Neurology*® Web site at Neurology.org and admission characteristics are shown in table 1. The mean ICU length of stay was 14 ± 8 days and the hospital length of stay was 20 ± 11 days. The majority (n = 197, 86%) of patients survived or remained inpatients long enough to complete 3 phases of study. The 229 SAH patients in this study underwent 743 serial IDC, CRP, TTR, and UUN measurements.

Table 1 Baseline characteristics of hospital-acquired infections in subarachnoid hemorrhage patients

	Hospital-acquired infection		
Admission characteristics	No (n = 176)	Yes (n = 53)	*p* Value
Women	109 (62)	35 (66)	0.63
Age, y	52 (14)	62 (15)	<0.001
Ethnicity			0.89
Black	46 (26)	11 (21)	
White, non-Hispanic	60 (34)	19 (35)	
White, Hispanic	62 (35)	20 (39)	
Asian	8 (5)	3 (6)	
Medical history			
Hypertension	83 (48)	31 (59)	0.2
Diabetes mellitus	19 (11)	7 (13)	0.63
Body mass index, kg/m^2	29 (6)	30 (8)	0.44
APACHE II score	13 (7)	18 (8)	<0.001
Glasgow Coma Scale	14 (9, 15)	9 (6, 14)	<0.001
Aneurysm clipping	116 (66)	40 (76)	0.2
Hunt Hess grade			<0.001
1, 2: Headache	93 (53)	11 (21)	
3: Stupor	44 (25)	12 (23)	
4: Obtunded	21 (12)	17 (32)	
5: Coma	18 (10)	13 (25)	
Modified Fisher score			<0.001
1: Thin clot	38 (22)	4 (8)	
2: Thin clot and IVH	11 (6)	5 (9)	
3: Thick clot	100 (57)	25 (47)	
4: Thick clot and IVH	27 (15)	19 (36)	

Abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; IVH = intraventricular hemorrhage.
Comparison of admission characteristics of study patients by the development of hospital-acquired infections.

Measurements of nutritional intake, nitrogen balance, and energy expenditure. The 14-day mean REE and caloric intake was 1,679 ± 608 calories/day and 846 ± 437 calories/day (11.3 ± 7.0 calories/kg/day), respectively. Protein intake was 32.6 ± 23.6 g/day and UUN was 10.7 ± 5.9 g/day, resulting in a mean nitrogen balance (NBAL) of −8.8 ± 6.1 g/day. Nutritional values broken down by phase of study can be found in table e-1. The mean TTR level was 19.4 ± 5.9 mg/dL, and mean CRP level was 6.0 ± 3.7 mg/dL. High mean CRP levels correlated with a higher Hunt Hess grade[21] (Spearman $r = 0.44$, $p < 0.001$) and modified Fisher score[22] ($r = 0.26$, $p < 0.001$), whereas low mean TTR levels were correlated with a higher Hunt Hess grade (Spearman $r = -0.41$, $p < 0.001$) and modified Fisher score ($r = -0.16$, $p = 0.02$).

At the time of IDC and NBAL assessments, 53% of the patients were receiving nutrition orally (872 ± 540 calories/day), while 37% of patients were being fed enterally (817 ± 606 calories/day), and 10% were NPO (223 ± 304 calories/day). In patients requiring propofol for sedation, the contribution toward daily caloric intake was 354 ± 254 calories/day. No patient received parenteral nutrition. The caloric intake was higher in those patients being mechanically ventilated (12.0 ± 7.1 calories/kg/day vs 10.8 ± 5.5 calories/kg/day, $p = 0.03$).

In multivariable linear regression, the 14-day negative NBAL was associated with lower caloric intake ($p < 0.001$), aneurysm clipping ($p = 0.03$), body mass index ($p = 0.001$), and CRP:TTR ratio ($p = 0.03$). A higher mean 14-day REE was associated with male sex ($p < 0.001$), younger age ($p < 0.001$), Hunt Hess grade ($p = 0.001$), and modified Fisher score ($p = 0.01$).

Outcome assessments. DCI was observed in 48 (21%) patients and was associated with a higher mean VO_2 (265 ± 85 mL/min vs 200 ± 48 mL/min, $p = 0.04$) and REE (27 ± 14 calories/kg vs 22 ± 8 calories/kg, $p = 0.01$) but not with mean TTR levels, caloric intake, or NBAL.

HAIs developed in 53 patients (23%) on mean PBD 8 ± 3. Pneumonia (33%) was most common, followed by urinary tract infection (21%). The mean negative NBAL was greater in subjects developing HAI (−11.5 ± 5.7 g/day vs 8.0 ± 6 g/day, $p < 0.001$). In a time to first HAI analysis, lower caloric intake (<11.3 calories/kg/day, $p = 0.02$) and greater

negative NBAL (>8.8 g/day, $p = 0.001$) were both associated with the development of HAIs (figure 1). In a multivariate Cox proportional hazards model, older age ($p = 0.002$), higher Hunt Hess score ($p < 0.001$), lower caloric intake ($p = 0.001$), and negative NBAL ($p = 0.04$) predicted time to first HAI (table 2).

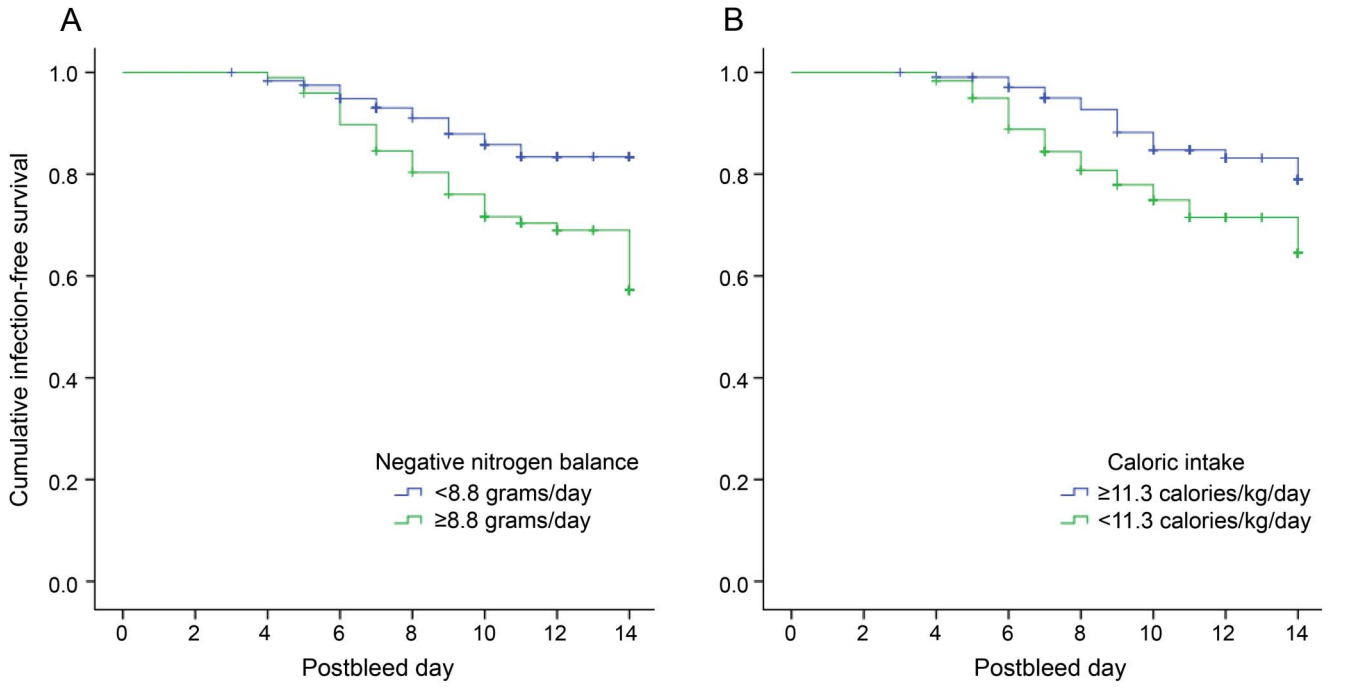
The median mRS score at 3 months was 3 (interquartile range 2, 4) with a mortality of 7% (n = 13) in the first 14 days. As shown in figure 2, TTR levels were a negative predictor of poor outcome at 3 months ($p < 0.001$), whereas mean CRP levels were directly associated with poor outcome ($p < 0.001$). The ratio of the mean CRP to TTR levels was found to be a stronger predictor than either marker alone (figure 2). In a multivariate logistic regression analysis adjusting for caloric intake, female sex, and modified Fisher score, the Hunt Hess grade, age, body mass index, DCI, mean 14-day NBAL, mean CRP:TTR ratio, and HAIs were independently associated with poor outcome 3 months after SAH (Nagelkerke $R^2 = 0.537$) (table 3).

DISCUSSION In this prospective observational study of metabolism and nutritional status, we identified factors that influenced the metabolic response and related protein catabolism, as well as those nutritional factors that influenced the development of HAIs and functional recovery after SAH. Malnutrition, characterized by underfeeding and protein catabolism, was found to be common and associated with HAIs in the first 2 weeks after SAH. The inflammation-mediated catabolic state was noted to have a widespread and sustained impact as noted by the influence of both net negative nitrogen balance and the CRP:TTR ratio on poor global recovery 3 months after SAH.

The metabolic rate after injury was associated with younger age and male sex, both factors that are well known to impact the REE across all acute and chronic illnesses.[23,24] We additionally identified an independent relationship between 2 measures of severity of SAH, the Hunt Hess score[21] and modified Fisher grade,[22] and metabolic rate. It is likely that this relationship is mediated by a surge of catecholamines and release of proinflammatory cytokines that occurs at the time of injury,[25–27] and we did find a modest correlation between CRP and TTR levels with both grading scales. Similar to other studies, we found high mean CRP levels in the acute setting to be a predictor of poor long-term recovery after SAH.[28,29]

By contrast, levels of TTR and their relationship to outcome after SAH have not been reported previously. TTR is often reported to be a biomarker of responsiveness to nutritional support; however, levels are influenced by inflammation and more accurately assess the impact of inflammation on the nutritional status.[30,31] Accordingly, previous studies, primarily in multiorgan failure and chronic renal failure patients, have utilized ratios of CRP to TTR in an

Figure 1 Kaplan-Meier curves for hospital-acquired infections



Survival curves demonstrate infection-free survival. (A) Comparison of groups across mean negative nitrogen balance. (B) Comparison of groups across mean caloric intake.

Table 2 Predictors of hospital-acquired infections after subarachnoid hemorrhage

Predictor	Hazard ratio	95% Confidence interval	*p* Value
Hunt Hess grade	1.64	1.29, 2.1	<0.001
Caloric intake[a]	0.91	0.86, 0.96	0.001
Negative nitrogen balance[b]	1.04	1.01, 1.08	0.043
Age, y[c]	1.03	1.01, 1.05	0.002

Results from a multivariable Cox proportional hazards model analyzing factors independently associated with the time to hospital-acquired infection. An additional variable not shown and that did not reach statistical significance ($p < 0.05$) is the modified Fisher score.
[a] Represents hazard ratio for every calorie/kg/day.
[b] Represents hazard ratio for every g/day.
[c] Represents hazard ratio for every year.

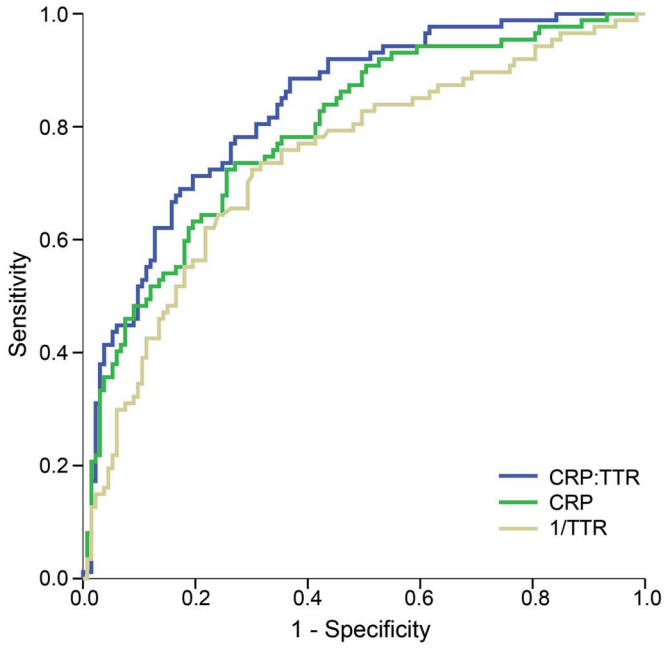
attempt to better understand nutritional changes in the setting of active inflammatory states.[32,33] We calculated a ratio of CRP to TTR for similar reasons, and found the combination of a high CRP and low TTR was a more sensitive indicator of 3-month outcome than either marker alone. Both the CRP:TTR ratio and negative NBAL levels remained independent predictors of poor outcome at 3 months in multivariate analysis, indicating the importance of inflammation-mediated protein energy malnutrition acutely after SAH.

We recognize that both CRP and TTR are considered nonspecific markers of inflammation and believe more detailed analyses of serum amino acids (e.g., glutamine) and cytokines would be necessary to more clearly define the interaction between the severity of injury, inflammation, and metabolic rate. Taken together, findings from this and our previous studies[6,17] indicate that the metabolic sequelae, protein catabolism, and free fatty acid metabolism seen after SAH are closely linked to the acute inflammatory response.

Malnutrition was not only influenced by inflammation. Despite initiating within 24 hours of admission, we routinely failed to meet both total calorie and protein requirements as indicated by IDC and NBAL measurements. This is consistent with other published reports on delivery of calories in ICUs.[34] It is likely that several of our unmeasured institutional practices of holding enteral nutrition prior to nongastric surgical procedures or for arbitrary levels of gastric residuals contributed to underfeeding. Contrary to our assumptions, those who received the lowest caloric intake were those patients who were not mechanically ventilated. There are 2 important implications of this finding. First, our underfeeding in nonventilated patients was likely the result of our institutional policy of discouraging enteral nutrition in those who are awake and potentially able to take oral nutrition. However, these patients often have significant dysphagia due to inattention or decreased appetites, resulting in undernourishment. This subset of patients requires more attention to their caloric intake and may benefit from enteral supplementation to their oral diet. Second, similar to a previous study,[6] a significant component of the additional calories in our mechanically ventilated patients came from propofol infusions, which is comprised predominantly of omega 6 fatty acids.[35] It is unclear what impact this may have upon nutrition-related outcomes.

Several strengths and limitations of our study are worth mentioning. Although this was a single-center observational study, we believe our practices are consistent with consensus guidelines[36] and a recent survey of North American ICUs,[37] allowing for generalizability of our results. We hypothesized that the metabolic response and nutritional status after SAH would be dependent on the inflammatory status, and our decision to allocate measurements into phases by PBD was based on previous reports of inflammatory response after SAH.[17,38] While this may have introduced measurement bias into our results, we believe our overall method of repeating

Figure 2 Receiver operating characteristic curve for C-reactive protein and transthyretin predicting poor outcome at 3 months



Area under the curve

Variables	Area	Std. error[a]	*P* value	95% Confidence interval	
				Lower bound	Upper bound
1/TTR[b]	.740	.035	<0.001	.671	.808
CRP[c]	.794	.031	<0.001	.734	.854
CRP:TTR	.835	.027	<0.001	.782	.888

Comparison of receiver operating characteristic curves and area under the curve for the ability of the C-reactive protein, transthyretin, and C-reactive protein to transthyretin ratio to predict poor outcome defined as a modified Rankin Scale score >3 at 3 months after subarachnoid hemorrhage. [a] Standard error: under the nonparametric assumption. [b] TTR = transthyretin. [c] CRP = C-reactive protein.

Table 3 Predictors of poor outcome 3 months after subarachnoid hemorrhage

Predictor	Odds ratio	95% Confidence interval	*p* Value
Hunt Hess grade	2.46	1.68, 3.60	<0.001
Age, y	1.08	1.04, 1.11	<0.001
Body mass index, kg/m^2	0.92	0.86, 0.99	0.03
Delayed cerebral ischemia	3.00	1.07, 8.42	0.04
Hospital-acquired infection	2.59	1.14, 5.89	0.03
Negative nitrogen balance	1.10	1.02, 1.19	0.01
CRP:TTR ratio	1.04	1.02, 1.06	0.04

Abbreviation: CRP = C-reactive protein; TTR = transthyretin.
Results from a multivariable logistic regression analyzing factors independently associated with poor outcome 3 months after SAH, identified as a modified Rankin Scale score >3. Negative nitrogen balance and CRP:TTR ratio represent the mean value at 14 days postbleed. Additional variables not shown in the table and that did not reach statistical significance ($p < 0.05$) include sex and modified Fisher score.

measures every 48–72 hours in the first 14 days after hemorrhage has resulted in a more robust analysis than previous reports that have relied on singular or infrequent measures of energy expenditure or NBAL assessments.[8,9]

We meticulously assessed caloric intake, accounting for oral, enteral, or IV intake, which allowed for accurate assessments of both protein and total caloric intake, and hence nitrogen balance. Protein catabolism is often reported using nitrogen balance, but it is increasingly recognized that serum measurements of micronutrients provide a more detailed analysis of nutritional status.[39] Likewise, both CRP and TTR are widely used but crude measures of inflammation-mediated nutritional status.[30] Future studies should focus on the interaction between specific inflammatory pathways and micronutrients.

The mRS is often used in studies of SAH, but may not be the most appropriate outcome when assessing the impact of inflammation-mediated malnutrition. Tools that are more detailed in the assessments of both cognitive status and exercise intolerance may provide more meaningful insight into the impact of inflammation-mediated malnutrition after SAH.[40,41]

A composite view of our results indicates that malnutrition, related to underfeeding and inflammation-mediated protein catabolism, is prevalent after SAH and associated with short-term secondary injury and long-term poor outcome. Aspects related to undernutrition may be modifiable, though recent studies indicate that the overall amount of caloric delivery may not be as important as specific substrate delivery. In previous studies, we and others have identified the importance of assessing free fatty acid metabolism and supplementation on the occurrence of DCI.[18,42,43] Protein energy malnutrition identified in this study may be another target for intervention with amino acid supplementation. Prospective studies assessing the impact of specific amino acids and inflammation on outcome are needed to determine whether immunomodulation with nutritional supplementation may provide benefit after SAH.

AUTHOR CONTRIBUTIONS

Dr. Badjatia: drafting/revising the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data; study supervision or coordination. A. Monahan: drafting/revising the manuscript for content, including medical writing for content; acquisition of data. A. Carpenter: drafting/revising the manuscript for content, including medical writing for content; acquisition of data. J. Zimmerman: drafting/revising the manuscript for content, including medical writing for content; acquisition of data. Dr. Schmidt: drafting/revising the manuscript for content, including medical writing for content; analysis or interpretation of data. Dr. Claassen: drafting/revising the manuscript for content, including medical writing for content. Dr. Connolly: drafting/revising the manuscript for content, including medical writing for content. Dr. Mayer: drafting/revising the manuscript for content, including medical writing for content; analysis or interpretation of data. Dr. Karmally: drafting/revising the manuscript for content, including medical writing for content; acquisition of data; study supervision or coordination. Dr. Seres: drafting/revising the manuscript for content, including medical writing for content; analysis or interpretation of data; study supervision or coordination.

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