Cerebrospinal Fluid Catecholamine Levels as Predictors of Outcome in Subarachnoid Hemorrhage

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Key Words

Subarachnoid hemorrhage • Sympathetic nervous system • Catecholamines • Cerebrospinal fluid • Prognosis • Outcome

Abstract

Objective: Subarachnoid hemorrhage (SAH) is associated with marked sympathetic activation at the time of ictus. The purpose of this study is to determine whether early central catecholamine levels measured from cerebrospinal fluid (CSF) relate to outcome in patients with SAH. **Methods:** Observational study of consecutive SAH grade 3–5 patients who underwent ventriculostomy placement, but did not undergo open craniotomy for aneurysm obliteration. CSF samples were obtained during the first 48 h following symptom onset and assayed for catecholamine levels. Statistical analyses were performed to determine whether the levels predicted mortality by day 15 or mortality/disability by day 30. **Results:** For the 102 patients included, mean age was 58, and 73% were female – 21% experienced day-15 mortality, and 32% experienced mortality/disability by day 30. Early mortality was related to Hunt-Hess (H/H) grade ($p < 0.001$), neu-

rogenic cardiomyopathy (NC) ($p = 0.003$), cerebral infarction ($p = 0.001$), elevated intracranial pressure (ICP) ($p = 0.029$), epinephrine (EPI) level ($p = 0.002$) and norepinephrine/3,4-dihydroxyphenylglycol (NE/DHPG) ratio ($p = 0.003$). Mortality/disability was related to H/H grade ($p < 0.001$), NC ($p = 0.018$), infarction ($p < 0.001$), elevated ICP ($p = 0.002$), EPI ($p = 0.004$) and NE/DHPG ($p = 0.014$). Logistic regression identified age [OR 1.09 (95% CI 1.01–1.17)], H/H grade [9.52 (1.19–77)], infarction [10.87 (1.22–100)], ICP elevation [32.26 (2–500)], EPI [1.06 (1.01–1.10)], and (inversely) DHPG [0.99 (0.99–1.00)] as independent predictors of early mortality. For mortality/disability, H/H grade [OR 21.74 (95% CI 5.62–83)], ICP elevation [18.52 (1.93–166)], and EPI [1.05 (1.02–1.09)] emerged as independent predictors. Proportional-hazards analysis revealed age [HR 1.041 (95% CI 1.003–1.08)], H/H grade [6.9 (1.54–31.25)], NC [4.31 (1.5–12.35)], and EPI [1.032 (1.009–1.054)] independently predicted early mortality. **Conclusions:** CSF catecholamine levels are elevated in SAH patients who experience early mortality or disability. EPI may potentially serve as useful index of outcome in this population of patients with SAH.

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Introduction

Biological molecular markers are being increasingly tested and employed in the diagnostic and prognostic evaluation of patients with cerebrovascular diseases [1, 2]. Biomarkers have been evaluated and utilized in the diagnosis of cerebral ischemic and hemorrhagic events [3], in predicting hemorrhagic complications from fibrinolytic therapy, in predicting an aggressive clinical course for middle cerebral artery infarctions, and in determining outcome [1, 2].

Early prognostication for patients with intracranial hemorrhage may provide crucial information regarding treatment options and family decisions. For patients with intracerebral hemorrhage (ICH) grading scales incorporating proven demographic, clinical and radiological predictors of mortality have been developed and validated for determining outcome [4, 5]. By contrast, no analogous validated multifactorial grading scale exists for reliably predicting outcome among patients with subarachnoid hemorrhage (SAH).

SAH is associated with sudden profound sympathetic activation [6], which may promote systemic inflammation [7], precipitate thrombotic processes [8], and cause cardiopulmonary dysfunction [9], all of which contribute to adverse outcomes in cerebrovascular disease [10, 11]. Inflammatory, thrombotic and cardiovascular biomarkers have previously been investigated as potential predictors of outcome in patients with SAH. The purpose of this study is to determine whether measures of acute central catecholamine activity may also serve as markers and predictors for early mortality and disability in patients with SAH.

Methods

Study Overview, Data Collection, Primary Endpoints

This investigation is an observational study of consecutive patients with primary nonrecurrent SAH. Demographic, clinical, radiologic, and laboratory data were abstracted from the medical record or obtained from family interviews. During the first 48 h following the ictus, all enrolled patients underwent cerebral spinal fluid (CSF) sampling for analysis. The primary endpoints were early mortality occurring by day 15, and poor outcome defined as mortality or disability with a Glasgow Coma Scale score of ≤ 10 by day 30 [12]. Glasgow Coma Scale assessments are routinely performed every 2 h on all service patients.

Inclusion/Exclusion Criteria

Inclusion criteria included age ≥ 18 years; clinical Hunt-Hess (H/H) grade 3–5 upon presentation; insertion of a functioning ventriculostomy drain; endovascular aneurysmal treatment

(open surgery not performed); collection of CSF within 48 h of onset, and informed consent. Exclusion criteria included preexisting severe cardiopulmonary disease; SAH due to trauma, arteriovenous malformation, ICH, arterial dissection or unusual/atypical causes; recent or distantly recurrent SAH; and prior placement of a ventriculoperitoneal (or ventriculopleural) shunt.

CSF Collection and Catecholamine Assay

All CSF samples were obtained by ventriculostomy drainage, following the waste of any CSF already present in the tubing. Using standard tubing systems with a drainage port of fixed distance from the ventriculostomy catheter, aspiration of 1 ml consistently removes all intraluminal CSF and allows for subsequent sample acquisition directly from the ventricular system. CSF samples (1 ml) were collected in a glass red-top-tube and immediately placed in a deep freeze at -80°C . After defrosting and brief centrifugation, 0.3-ml aliquot samples of supernatant were assayed by high performance liquid chromatography for several catecholamine compound and metabolite levels – epinephrine (EPI), norepinephrine (NE), 3,4-dihydroxyphenylglycol (DHPG), 3,4-dihydroxyphenylalanine (DOPA), dopamine (DA), 3,4-dihydroxyphenyl acetic acid (DOPAC) – using a previously described technique [13].

Data Grouping

Due to the low number of H/H grade 5 patients, grades 4 and 5 were grouped and the clinical grade variable was dichotomized between grade 3 and grade 4/5 for all calculations. Admission CT scans were scored for quantification of hemorrhage using the technique developed by Frontera et al., which provides the most linear correlation between radiographic severity and risk for complications and adverse outcomes [14]. Due to a disproportion in the distribution of CT scores, scores 1 and 2 and scores 3 and 4 were combined, respectively, and the radiological score variable was dichotomized between scores 1/2 and 3/4 for all calculations.

SAH Complications

Neurogenic cardiomyopathy (NC) was determined using transthoracic echocardiography performed within 2 days of onset, and was defined by characteristic myocardial dysfunction not conforming to a single vascular territory or attributable to any alternative process, demonstrating partial or complete resolution on repeat transthoracic echocardiography several days later [15]. Vasospasm was identified using transcranial ultrasound, which is routinely performed twice daily in all patients, and defined according to the following mean velocities (V_m) and velocity ratios (V_r) – middle cerebral artery $V_m > 120$ cm/s plus middle cerebral artery/internal cerebral artery $V_r > 3$, and anterior cerebral artery $V_m > 100$ [16, 17]. Infarction was defined as any acute arterial territorial infarct developing at any time during hospitalization as determined by cerebral CT imaging. Continuous ICP monitoring was performed via the inserted ventriculostomy catheter, which was maintained closed and opened only for reasons of ICP reduction or acquisition of laboratory samples. ICP elevation was defined as pressures persistently above 20 mm Hg for at least 10 min, not remedied by simple maneuvers such as head elevation or ventriculostomy drainage, and requiring aggressive intervention for normalization (ex hyperosmolar agents, sedation or hypothermia), at any time during hospitalization.

Statistical Analyses

For comparisons of categorical variables, the Fisher's exact test or χ^2 tests were used, and for comparisons of continuous variables the independent (two-tailed) t test and nonparametric rank sum tests were used. Catecholamine variables were interrogated for collinearity using appropriate statistical diagnostic tests. Variables demonstrating a possible association in the univariate analyses ($p < 0.1$) were entered into logistic regression models using the stepwise backward elimination method. All variables revealing a possible association ($p < 0.1$) with mortality were entered into Cox proportional (hazards) regression models using stepwise backward elimination. For all analyses, a p value < 0.05 was considered statistically meaningful. Outcome measures were presented according to assay level or ratio quartiles, and corresponding receiver operating characteristic (ROC) curves, and proportional-hazards survival curves, were constructed.

Study Location, Approval and Ethics

Eligible and enrolled patients were all admitted to the neurological intensive care unit at the Jefferson Hospital of Neurosciences. The present study was approved by the Committee on Human Research at Thomas Jefferson University Medical Center, and informed consent was obtained from all patients or family members for the acquisition of CSF samples. Laboratory researchers assaying CSF catecholamine levels were unfamiliar with the demographic, clinical or radiologic details of the patients, or with the occurrence of any of the primary-outcome measures.

Results

To obtain the study group, a total of 353 patients were screened. From these, 161 were excluded due to low SAH grade (H/H 1/2) or lack of need for ventriculostomy (H/H 3 without hydrocephalus), 35 were excluded due to moribund condition and/or discontinuation of support, 14 presented more than 48 h after onset, 4 had atypical reasons for SAH (2 endocarditis and 2 dissections), 4 were screened too late, 3 had preexisting severe cardiac problems (2 cardiomyopathies and 1 severe pulmonary hypertension), 2 refused enrollment, 1 was a previously treated rehemorrhage, and 1 had a preplaced ventriculoperitoneal shunt. Of the remaining patients, 25 had undergone surgical clipping of aneurysm, and 1 had insufficient CSF sample for assay.

For the 102 patients included, mean age was 58, and 73% were female. Baseline features of the study group are presented in table 1. Details regarding neurological condition, day of mortality or final clinical assessment are provided in table 2. Of the entire group, 21% experienced early mortality, and 32% experienced early mortality or disability. In the univariate analysis, early mortality was related to H/H grade ($p < 0.001$), NC ($p = 0.003$), infarction ($p = 0.001$), and elevated ICP ($p = 0.029$). Early mor-

Fig. 1. Proportion of patients experiencing early mortality or mortality/disability at every quartile of EPI level and NE/DHPG ratio. **a** Mortality by EPI quartile. **b** Mortality/disability by EPI quartile. **c** Mortality by NE/DHPG quartile. **d** Mortality/disability by NE/DHPG quartile. Figures illustrate greatest mortality (**a**) and mortality/disability (**b**) rates in the highest quartile of EPI level, with approximately twice as many adverse outcomes within the 4th quartile ($p = 0.005$ and $p = 0.003$ for the χ^2 linear association statistic). For the NE/DHPG ratio, an incremental increase in mortality (**c**) and mortality/disability (**d**) rates is observed at each subsequent quartile ($p = 0.012$ and $p = 0.018$ for the χ^2 test linear association statistic).

tality or disability was related to H/H grade ($p < 0.001$), NC ($p = 0.018$), infarction ($p < 0.001$) and elevated ICP ($p = 0.002$).

The timing of CSF collection was comparable between the groups (table 3). All samples were successfully assayed, for a total of 612 measurements. In the univariate analysis, early mortality was positively associated with EPI levels ($p = 0.002$) and NE/DHPG ratio ($p = 0.003$). Similarly, early mortality or disability was positively associated with EPI levels ($p = 0.004$) and NE/DHPG ratio ($p = 0.014$). The proportion of patients experiencing early mortality or mortality/disability for each quartile of EPI level and NE/DHPG ratio is illustrated in figure 1, and the respective ROC curves are illustrated in figure 2.

Table 1. Demographic, clinical, radiologic, and anatomical characteristics of the study groups

	Mortality (n = 21)	Disability (n = 12)	Mortality/ disability (n = 33)	No mortality/ disability (n = 69)	p value
Demographics					
Age, years	63 ± 15	56 ± 18	60 ± 16	56 ± 13	0.062/0.216
Female	62 (13)	75 (3)	67 (22)	77 (53)	0.175/0.277
Caucasian	62 (13)	25 (9)*	49 (16)	62 (43)	0.672/0.186
Medical history					
Hypertension	71 (15)	75 (9)	73 (24)	57 (39)	0.306/0.115
Tobacco use	62 (13)	50 (6)	58 (19)	61 (42)	0.826/0.751
EtOH use	0	8 (1)	3 (1)	6 (4)	0.308/0.477
Drug use	0	8 (1)	3 (1)	3 (2)	0.497/0.695
Cardiac disease	19 (4)	8 (1)	15 (5)	9 (6)	0.163/0.255
SAH aspects					
H/H grade 4/5	91 (19)	75 (9)**	85 (28)	22 (15)	<0.001/<0.001
CT score 3/4	79 (15)	67 (8)	74 (23)	55 (38)	0.075/0.070
Anterior aneurysm location ¹	53 (9)	83 (10)	66 (19)	78 (46)	0.061/0.212
Rehemorrhage	5 (1)	17 (2)	9 (3)	4 (3)	0.641/0.297
Complications					
Neurogenic cardiomyopathy ¹	38 (8)	8 (1)	27 (9)	9 (6)	0.003/0.018
Vasospasm ¹	50 (9)	75 (9)	60 (18)	69 (43)	0.103/0.374
Infarction	52 (11)	50 (6)**	52 (17)	12 (8)	0.001/<0.001
Intracranial hypertension	24 (5)	25 (3)*	24 (8)	3 (2)	0.029/0.002
Hospitalization					
Duration, days	7 ± 3	27 ± 4**	14 ± 11	20 ± 5	<0.001/0.004

For continuous variables, values represent means ± SDs, and statistical calculations performed using the nonparametric rank-sum test. For categorical variables, values represent percentages (n shown in parentheses). 'Drug use' refers to sympathomimetic agents, and 'Cardiac disease' refers to history of coronary artery disease/myocardial infarction or preexisting structural myocardial dysfunction. 'Mortality/disability' was defined as a Glasgow Coma Scale score ≤10 upon discharge from the neurological intensive care unit or adjoining intermediate care unit. Analyses performed include mortality versus no mortality, disability versus no mortality or disability, and mortality/disability versus no mortality/disability. p values are for 1st/3rd analyses, whereas for 2nd analysis, * indicates $p < 0.05$ and ** indicates $p < 0.01$.

¹ Angiogram was negative or not done in 14 cases, transthoracic echogram was uninterpretable in 2 cases (inadequate window), and no transcranial ultrasounds were recorded in 10 cases (inadequate windows).

Logistic regression (table 4) demonstrated positive associations between mortality and posterior aneurysm location ($p = 0.034$) and NC ($p = 0.002$), while age [OR 1.09 (95% CI 1.01–1.17)], H/H grade [9.52 (1.19–77)], infarction [10.87 (1.22–100)], ICP elevation [32.26 (2–500)] and EPI [1.06 (1.01–1.10)] emerged as independent predictors, and DHPG emerged as a negative predictor [0.99 (0.99–1.00)]. For the outcome of mortality/disability, NC ($p = 0.019$), infarction ($p < 0.001$), and NE/DHPG ($p = 0.003$) demonstrated positive associations, while H/H grade [OR 21.74 (95% CI 5.62–83.33)], ICP elevation [18.52 (1.93–166)] and EPI [1.05 (1.02–1.09)] emerged as independent predictors.

The predictive value of EPI was confirmed and the multivariate analysis validated by the bivariate analyses, and by alternative regression models constructed. Alternate models included each pertinent clinical variable indi-

vidually entered along with EPI ($p = 0.001$ – 0.028 and $p < 0.001$ – 0.004), catecholamine variables DHPG and NE/DHPG with EPI ($p = 0.003$ and $p = 0.002$), and regression analyses with simultaneous entry of all variables ($p = 0.017$ and $p = 0.007$), for the two outcome measures. In similarly constructed models, NE/DHPG predicted or tended to predict mortality/disability when entered with each individual pertinent clinical variable ($p = 0.006$ – 0.077).

For the time-dependent outcome of mortality, Cox proportional (hazards) regression analysis (table 5) reinforced the association between mortality and age [HR 1.041 (95% CI 1.003–1.080)], H/H grade [6.90 (1.54–31.25)], and EPI [1.032 (1.009–1.054)], and also revealed an association between NC and mortality [4.31 (1.50–12.35)]. The corresponding survival curves comparing EPI quartile groups are presented in figure 3.

Fig. 2. ROC curves for early mortality according to EPI level and NE/DHPG ratio, and for EPI level and H/H grade with a combined model. The figure illustrates the fair predictive value of EPI levels [AUC 0.72 (95% CI 0.60–0.85, $p = 0.002$)], and of the NE/DHPG ratio [AUC 0.71 (95% CI 0.55–0.84, $p = 0.003$)] for the outcome of early mortality. The figure also illustrates additive predictive value for early mortality when EPI levels and H/H grade [AUC 0.81 (95% CI 0.70–0.92, $p < 0.001$)] are entered in combination [AUC 0.89 (95% CI 0.82–0.95, $p < 0.001$)].

Discussion

In SAH, numerous biomarkers have been evaluated as potential predictors of outcome. Serum markers of inflammation [18], free-radical activity [19], coagulation function [20], cardiac injury [21] and neuronal injury [22]; CSF markers of inflammation [23], oxidation [24] and axonal damage [25]; cerebral microdialysate excitatory amino acid levels and markers of anaerobic metabolism [26]; urine albumin levels [27], and genetic profiles [28] have all been identified as possible outcome determinants following SAH. Complex interactions between different physiological systems may explain the diversity of biomarkers investigated as potential outcome predictors in SAH. Since intense sympathetic activation may initiate and participate in these various processes [7, 8], catecholamines may represent a valuable yet understudied group of biomarkers for predicting outcome.

Central sympathetic function is mediated by noradrenergic neurons in the locus ceruleus of the pons, and by the A_1 – A_2 noradrenergic and C_1 – C_3 adrenergic nuclear clusters in the ventrolateral medulla [29]. Studies have identified a prominent role for the C_1 – C_3 nuclei in mediating sympathetic output for chemoreceptor and baroreceptor cardiovascular reflexes [29], for activation of sympathoneural defensive responses by release of adrenomedullary catecholamines [29], for controlling physiological responses during physical exertion and exercise [29], and in the development of hypertension [30]. Conversely, the neurons of the A_1 – A_3 cluster activate the hypothalamic production and pituitary release of vasopressin and corticotiberin, and provide local inhibition to

Table 2. Final neurological condition and day of death or last clinical assessment

	Early mortality ¹	Mortality/disability	No mortality/disability
Number of patients	21	33	69
Day of death	7 (4–10)	–	–
Day of final clinical examination	7 (4–10)	10 (6–29)	20 (15–24)
Last GCS	4 (3–6)	6 (3–9)	15 (14–15)

Last GCS = Final Glasgow Coma Scale test performed on day of death or by day 30. Values represent medians (IQR shown in parentheses).

¹ Combinations of factors contributed to patient demise, including severe initial clinical presentation, intracranial hypertension, cerebral edema, cardiac dysfunction, cerebral ischemia, and rehemorrhage. The single most proximate process responsible for death involved persisting coma leading to discontinuation of support in 9 patients, marked ICH in 5 patients, global or focal cerebral edema in 2 patients, multiple or large cerebral infarctions in 2 patients, myocardial infarction with heart failure in 1 patient, cardiac arrest in 1 patient, and rehemorrhage causing clinical worsening and decision to discontinue support in 1 patient.

the adjacent C_1 – C_3 cells [29]. Via diffuse neocortical, limbic, thalamic and hypothalamic projections, the locus ceruleus primarily modulates global cerebral arousal, attention, vigilance, memory and behavior [29].

In the CNS, EPI and NE are metabolized to DHPG, given the presence of monoamine oxidase and the absence of catechol-O-methyltransferase [31]. NE/DHPG

Table 3. Timing of sample collections and catecholamine levels for the study groups

	Early mortality			Mortality/disability		
	mortality	no mortality	p value	mortality/ disability	no mortality/ disability	p value
Onset to collection, h	28 ± 15	28 ± 13	0.820	27 ± 14	28 ± 14	0.821
EPI, pg/ml	28.61 ± 26	11.86 ± 15.31	0.002	26.75 ± 27.38	9.83 ± 9.83	0.004
NE, pg/ml	168.04 ± 176.97	144.71 ± 124.06	0.548	179.40 ± 204.00	135.22 ± 85.01	0.966
DHPG, pg/ml	482.47 ± 367.02	652.66 ± 374.05	0.063	518.51 ± 350.47	665.02 ± 382.72	0.080
DOPA, pg/ml	1,024.5 ± 505.8	951.9 ± 438.1	0.378	1,027.8 ± 432.9	937.7 ± 459.9	0.108
Dopamine, pg/ml	132.46 ± 200.67	154.00 ± 416.59	0.611	146.31 ± 262.12	151.12 ± 428.71	0.362
DOPAC, pg/ml	12,880 ± 8,625	10,744 ± 6,693	0.356	12,632 ± 7,829	1,0491 ± 6,735	0.169
NE/DHPG	0.425 ± 0.273	0.368 ± 1.23	0.003	0.688 ± 1.91	0.233 ± 0.122	0.014

For continuous variables, values represent means ± SDs. p values calculated using the nonparametric rank-sum test.

Table 4. Logistic regression analyses for predictors of early mortality and mortality/disability

	Mortality				Mortality/disability			
	bivariate		multivariate		bivariate		multivariate	
	OR	p value	OR	p value	OR	p value	OR	p value
Age	1.04 (1.00–1.08)	0.051	1.09 (1.01–1.17)	0.024	–	–	–	–
H/H grade	23 (4.88–100)	<0.001	9.52 (1.19–77)	0.034	20 (6.62–62.5)	<0.001	21.74 (5.62–83.33)	<0.001
CT score	2.86 (0.87–9.35)	0.083	NS	–	3.85 (0.92–5.95)	0.074	NS	–
Anterior aneurysm	0.30 (0.09–0.91)	<0.034	NS	–	–	–	–	–
NC	6.41 (1.98–20.83)	0.002	NS	–	3.88 (1.25–12.05)	0.019	NS	–
Infarction	5.26 (1.88–14.71)	0.002	10.87 (1.22–100)	0.033	8.13 (2.97–22.22)	<0.001	NS	–
ICP elevations	4.74 (1.23–18.52)	0.024	32.26 (2–500)	0.015	10.75 (2.13–52.63)	0.004	18.52 (1.93–166)	0.011
EPI	1.04 (1.02–1.07)	0.002	1.06 (1.01–1.10)	0.009	1.05 (1.02–1.09)	0.001	1.05 (1.02–1.09)	0.004
DHPG	0.99 (0.997–1.00)	0.066	0.99 (0.99–1.00)	0.010	1.00 (1.00–1.00)	0.07	NS	–
NE/DHPG	NS	–	NS	–	49.38 (3.69–661)	0.003	NS	–

Multivariate logistic regression model for mortality incorporates age, H/H grade, CT score, aneurysm location, NC, infarction, elevated ICP, and the variables EPI, DHPG, NE/DHPG. Multivariate model for mortality/disability incorporates hypertension, H/H grade, CT score, NC, infarction, elevated ICP, and the variables EPI, DHPG, NE/DHPG. Values in parentheses are 95% CIs.

provides a relative measure of NE release to uptake, and serves as an index of active noradrenergic function [32]. In human subjects, plasma NE/DHPG progressively increases with increasing sympathetic stimulation [32], and CSF ratios increase with sympathetic disinhibition [33], while sympatholytics decrease the ratio in animal studies [34]. As a precursor in the synthesis of NE and EPI, DA represents an essential constituent for catecholaminergic compound production, and DA release increases in response to physiologic stress [35]. Similarly, it has been proposed that CSF levels of DOPA may reflect central catecholamine biosynthetic capacity [33], and that CSF

DOPAC levels may provide an estimate of overall central catecholamine transmission [36].

The results of our study demonstrate that CSF EPI levels independently predicted which patients died or were disabled from SAH, with a 3–6% increased risk for each picogram per milliliter increase in EPI. Results also indicate that EPI levels may contribute additively to H/H grade in a combined model for predicting early mortality. Our findings are consistent with those of a prior report, which identified elevated EPI and NE levels in the plasma and CSF of SAH patients with adverse outcomes [37]. This prior investigation was, however, limited by very

Table 5. Proportional-hazards analysis for the time-dependent outcome of mortality

	HR	p value
Age	1.041 (1.003–1.080)	0.034
H/H grade	6.90 (1.54–31.25)	0.012
CT score	1.50 (0.368–6.10)	0.573
Anterior aneurysm	0.662 (0.228–1.92)	0.448
NC	4.31 (1.50–12.35)	0.007
Infarction	2.47 (0.764–8.0)	0.131
ICP elevation	2.61 (0.574–11.90)	0.215
EPI	1.032 (1.009–1.054)	0.005

HR = Hazard ratio. Regression model incorporates variables age, H/H grade, CT score, aneurysm location, NC, infarction, elevated ICP, and EPI. Figures in parentheses are 95% CIs.

small patient numbers and a lack of rigorous statistical analysis [37]. Critics of that study also questioned whether the presence of EPI in the CSF may have been due to entry from the systemic circulation at the time of hemorrhage [38]. However, CSF EPI has also been detected and quantified in various (nonhemorrhagic) psychiatric [39], neurodegenerative [40], and pain-related conditions [41], and has been found to be increased in hyperactive states, such as anxiety or psychosis [42, 43], and decreased in despondent states including depression [44, 45].

The findings of our investigation are consistent with evidence in the literature linking sympathetic function with diverse systemic and multiorgan derangements, including hypertension [46], myocardial ischemia [47], congestive heart failure [48], cardiac tachyarrhythmias [49], sudden cardiac mortality [50], abnormal renal natriuresis [51], enhanced platelet aggregation [52] and impaired immune function [53]. Sympathetically mediated neurogenic cardiopulmonary complications have been related to adverse outcomes following SAH [54], and sympathetic activity has been connected to increased inflammation and enhanced thrombosis [7, 8], the markers of which predict detrimental outcomes in patients with SAH [18, 20]. Adrenergic activity has also been invoked in the production of cerebral vasospasm [55], although as in our study infarction may also occur independent of any spasm [56], as well as in the development of cerebral edema following ICH [57]. Thus, elevated catecholamine levels may induce a state of generalized multiorgan dysfunction, which promotes deleterious clinical outcomes beyond simply the extent of neurological impairment.

Fig. 3. Proportional hazards analysis survival curve. Adjusted cumulative survival by posthemorrhage day for patients in the highest (4th) quartile of EPI level versus those in the lower (1st–3rd) EPI quartiles. The figure illustrates consistently greater mortality rates among the 4th-quartile group over time [HR 2.72 (95% CI 1.01–7.30, $p = 0.048$)].

The findings of our research contribute to the prognostic armamentarium available for assessing outcome in patients with severe-grade SAH. However, our results may also serve to optimize subject selection for future sympatholytic trials, and thereby provide a new avenue for novel therapeutic strategies and interventions. Catecholamine receptor blockade has been proven advantageous in various hyperadrenergic cardiovascular states [46–49], and may also potentially improve outcomes in neurogenic cardiopulmonary processes [58]. As such, clinical biomarkers need not be used solely for prognostic information (or improperly employed to promote clinical nihilism), but instead may be utilized to advance medical research and present novel treatment opportunities.

Limitations to our study include specimen contamination by plasma, which may theoretically confound the measurement of central catecholamine analytes. However, SAH by nature involves hemorrhage into the CSF, making this an unavoidable consequence. The ineligibility of devastated SAH patients whose condition was immediately terminal or in whom support was discontinued early, thereby precluding ventriculostomy, may have excluded those patients with the greatest elevations in central catecholamine levels. Thus, our results may have underestimated the true differences in central catechol-

aminergic profiles between patients with and without adverse outcomes. The variable use of different anesthetic, sedating and analgesic agents at various doses and durations, and the absence of a standard continuous measure of intensity and duration of action, as well as the unquantifiable impact upon the sympathetic output in any given individual, may represent an additional drawback. A final limitation is the small size of our study in that larger subject numbers may have provided greater power and fidelity in identifying differences between the groups. Nevertheless, the narrow CIs for EPI indicate the precision of our ORs and results.

Positive aspects of our study include the consistency of our results with the existing literature regarding determinants of mortality and disability, including age [59, 60], severe clinical grade [59, 60], presence of neurogenic cardiomyopathy [9], cerebral infarction [59, 60], and ICP elevations [61]. Additional attributes include the plausibility of our findings, given the proven activation of the sympathetic nervous system following SAH [6], the established connection between sympathetic activity and systemic inflammation and thrombosis [7, 8], and the association between markers of inflammation and thrombosis with outcome [18, 20]. Our findings are also internally consistent, revealing elevations in several catecholaminergic parameters among patients with adverse outcomes. Finally, the absence of a contemporary study evaluating CSF catecholamine as potential biomarkers indicates the unique nature of our study.

Conclusion

In conclusion, SAH patients who die in hospital or who are disabled by 30 days demonstrate greater central activation of the sympathetic nervous system than those who survive without severe impairment. CSF catecholamine levels and ratios may serve as early indicators of clinical neurological outcome, and therefore may serve as valuable biomarkers in the prognostication of patients with SAH. Additional studies are needed to verify these findings.

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Disclosure Statement

The authors have no financial affiliations or conflicts of interest to announce.

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