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Predictors of unfavourable outcome in aneurysmal subarachnoid haemorrhage

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ABSTRACT

Background. Mortality rates following aneurysmal subarachnoid haemorrhage (aSAH) have decreased due to improvements in diagnoses and the management of complications, as well as early obliteration of the aneurysms. Neurogenic pulmonary oedema (NPO) is a clinical syndrome associated with an acute increase in intracranial pressure and a release of catecholamines into the circulation. This study investigated independent predictors of unfavourable outcomes (Glasgow Outcome Scores 1, 2 or 3) in patients with aSAH.

Materials and methods. A total of 262 patients with aSAH (162 females) were included in this prospective study. Clinical characteristics were assessed, and electrocardiographic, serum cardiac and inflammatory biomarker measurements were recorded on admission. Outcomes were assessed three months after admission. Univariate and multivariate analyses of these data were used to predict unfavourable outcomes.

Results. A total of 156 patients (59.54%) had unfavourable outcomes. Compared to those who had favourable outcomes, patients with unfavourable outcomes were significantly older (54.37 ± 10.56 *vs.* 49.13 ± 10.77 years; $p < 0.001$) and had more severe aSAHs (Hunt and Hess grades ≥ 3: 82.7% *vs.* 39.6%; $p < 0.001$). Patients with unfavourable outcomes were more likely to have NPO (10.3% *vs.* 2.8%; $p = 0.023$), hydrocephalus (34.0% *vs.* 20.8%; $p = 0.02$), and aneurysm reruptures (28.2% *vs.* 3.8%; $p < 0.001$). Independent predictors of an unfavourable outcome included Hunt and Hess grades ≥ 3 (odds ratio [OR], 4.291; 95% confidence interval [CI], 2.168–8.491; $p < 0.001$), increased systolic blood pressure on admission (OR, 1.020; 95% CI, 1.002–1.038; $p = 0.03$), increased heart rate (HR) on admission (OR, 1.024; 95% CI, 1.001–1.048; $p = 0.04$), and aneurysm rerupture (OR, 4.961; 95% CI, 1.461–16.845; $p = 0.01$).

Conclusions. These findings suggest that aneurysm reruptures, as well as increased blood pressure and HR, are associated with unfavourable outcomes in patients with aSAH.

Key words: subarachnoid hemorrhage, outcome, neurogenic pulmonary edema, hydrocephalus, rerupture

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Introduction

Aneurysmal subarachnoid haemorrhage (aSAH) predominantly affects young adults and results in premature death in approximately 40% of patients [11, 30, 38]. Survivors often require help with daily living [1]. Neurogenic pulmonary oedema (NPO) is a clinical syndrome associated with an acute increase in intracranial pressure and a release of catecholamines into the circulation. After traumatic brain injury, aSAH is the second most common cause of NPO [2, 6, 28]. Patients with aSAH who develop NPO have higher mortality rates than those who do not [17, 28, 35]. Hypertension (HTA) is the most common comorbid disease, with prevalence estimates exceeding 40% in some studies [18, 20, 41, 42]. No clear

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association between a premorbid history of HTA and aSAH outcome has been established [10, 18–20, 23]. We investigated the effects of NPO, HTA and other clinical variables on outcomes in patients with aSAH.

Materials and methods

Between August 2009 and January 2014, 262 consecutive patients who were admitted to the neurosurgery clinic were enrolled in the study. The inclusion criteria for the study were patients ≥ 18 years of age with an aSAH diagnosis confirmed using cerebral computed tomography (CT) scanning and CT angiography [24]. If the CT angiogram was negative but the suspicion of an aneurysm was high, CT angiography was repeated two days later. The time interval between aSAH onset and hospital admission was < 96 h. Chest X-rays of patients with suspected aSAH were obtained immediately. Patients with a history of myocardial infarction, cardiomyopathy or congestive heart failure were excluded from the study.

The study protocol was approved by the ethics committee of the School of Medicine, University of Belgrade (Belgrade, Serbia; no. 440/VI-11); informed consent was obtained from each patient or an appropriate designee. The identities of the patients were protected. All procedures were performed in accordance with relevant institutional guidelines and regulations. After enrolment, demographic and clinical data were collected by interviewing patients and their families and by reviewing medical records. These data included age, sex and risk factors for coronary artery disease. Heart rate (HR) and systolic blood pressure (SBP) measurements were recorded on admission. Neurological injuries were assessed for severity using the Hunt and Hess [12] and Fisher grades [7] recorded for each patient on admission. Patients classified as having Hunt and Hess grade I or II haemorrhages were admitted to the neurosurgery ward, whereas those with haemorrhages that were graded III–V were admitted to the neurosurgical intensive care unit (NICU).

Clinical management

For each patient, outcomes were determined three months after aSAH using the Glasgow Outcome Score (GOS) scale: 1 = death; 2 = persistent vegetative state; 3 = severe disability, conscious but disabled, dependent on others for daily support; 4 = moderate disability, disabled but independent, can work in a sheltered setting; and 5 = good recovery, resumption of normal daily living with minor deficits [16].

Patients with a GOS of 1, 2 or 3 were classified as having unfavourable outcomes, whereas those with a GOS of 4 or 5 were classified as having favourable outcomes.

Each patient was examined daily for signs of NPO using the clinical criteria described by Davison et al. [6], including abrupt respiratory distress (tachypnoea, dyspnoea or hypoxia [PaO_2/FiO_2 < 200]), the presence of bilateral crackles on auscultation, and the presence of frothy pink tracheal fluid. The radiographic criteria used to diagnose NPO included sharply defined bilateral pulmonary markings accompanied by blurring or haziness of the perivascular outlines and a loss of hilar shadow demarcation [28]. All chest X-rays were interpreted by board-certified radiologists who were blinded to the patients' clinical symptoms. The spontaneous resolution of pulmonary infiltrates occurred within 48 h. Patients who fulfilled all of these criteria were diagnosed with NPO. Arterial blood gas analyses were used to determine the type of respiratory support necessary. If inotropic or vasopressor support was necessary, we recorded when this was initiated. All NICU patients were monitored continuously using electrocardiography (ECG) and by recording noninvasive blood pressure measurements in accordance with standard clinical practice. Central venous catheters, but not pulmonary artery catheters, were used [11].

All procedures were performed in accordance with the relevant aSAH treatment guidelines and recommendations [4, 37, 38].

Electrocardiographic, serum cardiac and inflammatory biomarkers

Twelve-channel ECG was used on the day of each patient's enrolment to measure ST–T changes (e.g. ST depression or elevation, negative, biphasic or flattened T waves), the corrected Q–T wave (QTc) interval, rhythm disturbances and ventricular premature complexes. All electrocardiographic measurements were interpreted by board-certified cardiologists.

The following biomarkers for cardiac injury and inflammation were measured: creatine phosphokinase (CPK), CPK muscle/brain isoenzyme (CPK-MB), cardiac troponin I (TnI), and C-reactive protein (CRP). Total serum CPK and CPK-MB isoenzyme activities were measured using standard spectrophotometry. Serum TnI levels were measured using a chemiluminescence enzyme immunoassay. CRP was measured using turbidimetry. Biomarker levels were classified as elevated if they exceeded the following reference levels: CPK, 150 IU/L for women and 200 IU/L for men; CPK-MB, 24 IU/L; TnI, 0.04 ng/mL; and CRP, 5 mg/L. The time interval between the onset of aSAH symptoms and biomarker measurements was less than 96 h for every patient.

Neurological assessments

Every patient was neurologically assessed and clinical signs of hydrocephalus, delayed cerebral ischaemia (DCI) and aneurysm reruptures were recorded. CT scans were also performed if there were signs of neurological deterioration. The term 'vasospasm' is used for narrowing of the large cerebral arteries and DCI caused by cerebral infarction and/or neurological deterioration. The criteria for aneurysm rerupture were new clinical signs of neurological deterioration together with signs of new bleeding on a CT scan.

We only used clinical and radiological criteria (CT scans) to diagnose DCI and did not prove that this was due to vasospasm. Therefore, this data was not included in our analyses.

Statistical analyses

A total of 262 patients were dichotomised based on their three-month outcomes (unfavourable, GOS = 1–3 or favourable, GOS = 4–5). Categorical variables were expressed as frequencies and percentages, whereas continuous variables were expressed as means ± standard deviations. The Kolmogorov-Smirnov test was used to confirm that the data was normally distributed. For the unfavourable versus favourable group comparisons, chi-square and Fisher's exact tests were used for categorical variables, whereas unpaired *t*-tests and Mann-Whitney U tests were used for continuous variables. Univariate and multivariate logistic regression analyses were used to identify variables that predicted unfavourable outcomes. The data was analysed using SPSS software (ver. 22.0; IBM Corp., Armonk, NY, USA); a p-value < 0.05 was considered statistically significant.

Results

This study included 262 patients of whom 59.54% (156 patients) had unfavourable outcomes. A total of 368 patients with aSAH were assessed, and 106 patients (28.8%) were excluded. The reasons for exclusion were: 54 patients were admitted to hospital more than 96 h after aSAH onset, and 21, 16 and 15 patients had a history of myocardial infarction, cardiomyopathy, and congestive heart failure, respectively.

The mean ages of the 156 patients with unfavourable outcomes and the 106 patients with favourable outcomes were 54.37 and 49.13 years, respectively (p < 0.001; Tab. 1). A total of 63.5% of the patients with NPO were women, whereas 60.1% of the patients who did not have NPO were women (p = 0.04). A history of HTA was more common among patients with NPO (p = 0.001). There were significantly more patients with Hunt and Hess grades ≥ 3 among those with unfavourable outcomes than among those with favourable outcomes (p < 0.001). A comparison of radiological characteristics revealed a significant increase in the incidence of NPO among patients with Fisher grades > 2 (p < 0.001). In addition, the mean peak SBP and HR were significantly increased in patients with unfavourable outcomes (p < 0.001 and 0.007, respectively).

Electrocardiographic measurements showed that there were no significant differences in the ST–T or QTc interval between patients with favourable and unfavourable outcomes. It was not clear whether patients with unfavourable outcomes had more severe cardiac damage than patients with favourable outcomes. The mean CPK-MB levels were significantly increased in patients with unfavourable compared to those with favourable outcomes (15.3 ± 7.3 *vs.* 13.5 ± 6.6 IU/L; p = 0.04), but the mean TnI (0.246 ± 0.870 *vs.* 0.219 ± 0.822 ng/mL; p = NS) and CPK (143.8 ± 103.2 *vs.* 132.6 ± 93.2 IU/L; p = NS) levels were not. However, unfavourable outcomes were significantly more common among patients with elevated CPK levels (33.3% *vs.* 20.8%; p = 0.03). Mean CRP levels were not significantly increased in patients with unfavourable compared to those with favourable outcomes (6.56 ± 6.40 *vs.* 5.52 ± 4.48 mg/L; p = NS).

The neurological assessments showed that aneurysm reruptures and hydrocephalus were significantly more common among patients with unfavourable compared to those with favourable outcomes (p = 0.02 and < 0.001, respectively). Patients with favourable outcomes also had a significantly increased frequency of secured aneurysms (p < 0.001).

The GOSs of patients with aSAH showed that 36 patients (13.7%) recovered well, 32 (12.2%) had moderate disability, 83 (31.7%) had severe disability, 71 (27.1%) were in a persistent vegetative state, and 36 patients (13.7%) died. After univariate logistic regression analysis and adjustment using multivariate logistic regression (Tab. 2), we identified the following independent predictors of unfavourable outcomes: Hunt and Hess grades ≥ 3 (odds ratio [OR], 4.291 per quintile; 95% confidence interval [CI], 2.168–8.491; p < 0.001), aneurysm reruptures (OR, 4.961; 95% CI, 1.461–16.845; p = 0.01), increased SBP (OR, 1.020; 95% CI, 1.002–1.038; p = 0.03), increased HR (OR, 1.024; 95% CI, 1.001–1.048; p = 0.04), and unsecured aneurysms (OR, 9.377; 95% CI, 1.138–77.244; p = 0.04).

Discussion

A comparison of demographic characteristics revealed that patients with unfavourable outcomes were significantly more likely to have had a severe haemorrhage (Hunt and Hess grades III–V) than patients with favourable outcomes (Tab. 1) [17, 28, 35]. In our cohort of 262 patients with aSAH, the incidence of unfavourable outcomes was 59.5%. In a multicentre study performed by Galea et al. [9], 28.6% of the patients had unfavourable outcomes. The difference between these studies may be due to patients in the multicentre study having a better neurological status on admission. In the multicentre study, the haemorrhage severity scores of almost 70% of patients were World Federation of Neurosurgeons grade I or II on admission, whereas in our study 35% of patients had a Hunt and Hess severity grade of I or II. All patients with unfavourable outcomes had severe bleeding (Fisher grades III and IV) that was radiologically visible [47].

In contrast to previous studies, we did not find that a ruptured aneurysm in the posterior circulation was a risk factor for unfavourable outcomes [14, 28, 31]. If patients in this category died before they reached hospital, this may explain why we did not observe a significant effect. Previous studies have also described electrocardiographic abnormalities and myocardial enzyme release in patients with aSAH [3, 29, 39], but the effect of cardiac dysfunction on aSAH outcome remains unclear. Serum cardiac biomarkers have been used to predict

Table 1. Comparison of variables between aSAH patients with unfavourable and favourable outcomes

	Pts with unfavourable outcome N = 156	Pts with favourable outcome N = 106	P[b]
Age (mean ± SD), y	54.37 ± 10.56	49.13 ± 10.77	< 0.001[a]
Female sex, n (%)	99 (63.5)	63 (59.4)	NS
Clinical characteristics			
Hunt and Hess ≥ 3, n (%)	129 (82.7)	42 (39.6)	< 0.001[a]
SBP (mean ± SD), mmHg	156.57 ± 23.35	137.36 ± 21.28	< 0.001[a]
HR (mean ± SD), min^{-1}	84.29 ± 16.96	78.92 ± 14.03	0.007[a]
Admission on day of aSAH attack, n (%)	72 (55.8)	57 (53.8)	NS
NPO, n (%)	16 (10.3)	3 (2.8)	0.02[a]
Risk factors for CAD, n (%)			
History of hypertension	72 (46.2)	28 (26.4)	0.001[a]
History of smoking	31 (19.9)	35 (33.0)	0.02[a]
History of diabetes	27 (17.3)	19 (17.9)	NS
History of hyperlipidemia	44 (28.2)	33 (31.1)	NS
Family history of CAD	42 (26.9)	26 (24.5)	NS
Radiological characteristics			
Fisher > 2, n (%)	123 (78.8)	47 (44.3)	< 0.001[a]
Anterior circulation aneurysm location, n (%)	138 (88.5)	95 (89.6)	NS
Multiple aneurysms, n (%)	14 (9.0)	14 (13.2)	NS
ECG characteristics			
ST-T changes, n (%)	41 (26.3)	23 (21.7)	NS
ST depression, n (%)	22 (14.1)	7 (6.6)	NS
ST elevation, n (%)	19 (12.2)	11 (10.4)	NS
Negative T waves, n (%)	14 (9.0)	10 (9.4)	NS
Prolonged QTc interval, n (%)	30 (19.2)	11 (10.4)	NS
Ventricular premature complexes, n (%)	14 (9.0)	10 (9.4)	NS
Neurological characteristics			
Secured[c] aneurysm, n (%)	109 (69.9)	105 (99.1)	< 0.001a
Hydrocephalus, n (%)	53 (34.0)	22 (20.8)	0.02[a]
Rerupture, n (%)	44 (28.2)	4 (3.8)	< 0.001[a]
Seizures, n (%)	30 (19.2)	23 (21.7)	NS
Biohumoral characteristics			
Troponin I, (mean ± SD), ng/mL, median (IQR)	0.246 ± 0.870 0.021 (0.010–0.063)	0.219 ± 0.822 0.020 (0.011–0.054)	NS
Elevated troponin I, n (%)	50 (32.1)	32 (30.2)	NS
CPK (mean ± SD), IU/L, median (IQR)	143.8 ± 103.2 112.0 (68.5–213.0)	132.6 ± 93.2 103.5 (76.5–164.3)	NS
Elevated CPK, n (%)	52 (33.3)	22 (20.8)	0.03[a]
CPK-MB (mean ± SD), IU/L, median (IQR)	15.3 ± 7.3 14.0 (10.0–2.0)	13.5 ± 6.6 12.0 (8.0–17.0)	0.04[a]
Elevated CPK-MB, n (%)	18 (11.5)	9 (8.5)	NS
C-reactive protein (mean ± SD), mg/L median (IQR)	6.56 ± 6.40 4.95 (2.83–8.85)	5.52 ± 4.48 4.55 (2.88–6.95)	NS
Elevated C-reactive protein, n (%)	76 (48.7)	45 (42.5)	NS

aSAH — aneurysmal subarachnoid haemorrhage; NPO — neurogenic pulmonary oedema; SBP — systolic blood pressure; HR — heart rate; CAD — coronary artery disease; ECG —electrocardiography; SD — standard deviation; IQR — interquartile range; CPK — creatine phosphokinase; CPK-MB — creatine phosphokinase MB isoenzyme

[a]Statistically significant

[b]According to chi-square, Student's t-test or Mann-Whitney U test where appropriate

[c]All of 214 pts with secured aneurysm had aneurysm clipped, except three of them (all with unfavourable outcomes) whose aneurysms were coiled

Table 2. Multivariate logistic regression analysis to identify variables predictive of unfavourable outcome associated with aSAH

	Multivariate		
Predictor	**OR**	**95% CI**	**P**
Age, years	1.030	0.999–1.063	NS
Female sex	1.750	0.863–3.548	NS
Hunt and Hess grade ≥ 3	4.291	2.168–8.491	< 0.00[a]
History of HTA	0.749	0.349–1.606	NS
History of smoking	1.852	0.878–3.908	NS
NPO	2.104	0.433–10.215	NS
SBP	1.020	1.002–1.038	0.03[a]
HR	1.024	1.001–1.048	0.04[a]
Hydrocephalus	1.607	0.766–3.371	NS
Rerupture	4.961	1.461–16.845	0.01[a]
Unsecured aneurysm	9.377	1.138–77.244	0.04[a]
Prolonged QTc	0.757	0.266–2.154	NS
CPK-MB (IU/L)	1.006	0.954–1.061	NS

CI — confidence interval; OR — odds ratio; aSAH — aneurysmal subarachnoid haemorrhage; HTA — hypertension; NPO — neurogenic pulmonary oedema; SBP — systolic blood pressure; HR — heart rate; CPK-MB — creatine phosphokinase MB isoenzyme
[a]Statistically significant

negative outcomes [21, 22, 25, 43, 44, 46]. In our study, only mean CPK-MB levels were significantly increased in patients with unfavourable outcomes. Univariate logistic regression analysis revealed that increased levels of CPK-MB could predict unfavourable outcomes. A meta-analysis by Zhang et al. [46] showed that an increase in TnI was associated with an increased risk of poor outcome (OR 1.85; 95% CI 1.49–2.30).

In our study, electrocardiographic abnormalities did not occur more frequently in patients with unfavourable outcomes. A prolonged QTc interval did predict unfavourable outcomes in the univariate logistic regression analysis. However, neither of these variables was an independent predictor of unfavourable outcomes [13]. In many studies, NPO is associated with unfavourable outcomes [17, 28, 36]. However, in our study, NPO was not an independent predictor of unfavourable outcomes.

Multivariate logistic regression analysis revealed that Hunt and Hess grades, aneurysm reruptures, increased SBP and HR and unsecured aneurysms were independent predictors of unfavourable outcomes in patients with aSAH. Previous studies have shown that the only consistent and independent predictors of negative outcomes in aSAH patients are poor haemorrhage severity grades, older age, aneurysm reruptures, and DCI [27, 32, 33, 45].

Neurological status on admission to hospital reflects the severity of a brain injury at the time of rupture. This is the single most important predictor of outcomes in patients with aSAH [38, 45]. Jaja et al. [15] demonstrated that each one-point increase in neurological grade resulted in an approximately two-fold increase in the risk of a poor outcome at three months.

Many studies have shown that aneurysm rerupture is a strong predictor of outcomes in patients with aSAH [40]. Early treatment of a ruptured aneurysm is particularly important to reduce rebleeding [9]. In addition, an unsecured aneurysm, with or without rebleeding, is a predictor of poor outcomes in patients with aSAH because more aggressive measures (e.g. HTA and haemodilution therapy) can be used to prevent vasospasm in patients with a secured aneurysm.

In patients with aSAH, an association between HTA and outcomes has been supported by some studies [6, 18, 19, 34, 42] and questioned by others [6, 10, 20, 23, 26]. De Marchis et al. [5] found that patients with premorbid HTA had more severe initial bleeding and an increased risk of mortality while in hospital. Our study found that increased SBP, but not premorbid HTA, was a predictor of negative outcomes.

Zheng et al. [48] also showed that good control of premorbid HTA had a favourable effect on outcomes in patients with aSAH. Patients with uncontrolled HTA had more severe aSAH and haemorrhage grades than patients with well-controlled HTA. In addition, the patients with uncontrolled HTA included more frequent cases of aneurysm rebleeding, hydrocephalus and cerebral vasospasm, even after adjustment for age and poor Hunt and Hess grade.

However, we found that a history of premorbid HTA was not a predictor of unfavourable outcomes in aSAH patients. Increased HR on admission was an independent predictor of negative outcomes. Schmidt et al. [36] showed that a prolonged elevated HR was associated with major adverse cardiopulmonary events and poor outcomes in aSAH patients.

This study has some limitations. Firstly, different time intervals between the onset of aSAH and hospital admission may have influenced our results. Secondly, we excluded patients with a history of myocardial infarction, congestive heart failure and cardiomyopathy to investigate the incidence of NPO in patients with aSAH. This may also have influenced our results. Finally, we only recorded measurements once and this was within 96 h of aSAH onset. In total, 50.8% of these measurements were recorded after the initiation of aSAH therapy. Despite these limitations, this is the only study to have investigated the spectrum of clinical, radiological and biochemical variables that may be used to predict negative outcomes in patients with aSAH. The influence of aSAH treatment on these results should be assessed in more detail.

Conclusions

In patients with aSAH, the predictors of unfavourable outcomes include a high Hunt and Hess grade, aneurysm rerupture, and an unsecured aneurysm, as well as increased SBP or HR. NPO and premorbid HTA are not independent predictors of unfavourable outcomes.

Conflict of interest

The authors declare that they have no conflict of interest.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee, and in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent was obtained from all individual participants included in the study.

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