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## RESEARCH PAPER

# Early neurological deterioration after subarachnoid haemorrhage: risk factors and impact on outcome

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### ABSTRACT

**Background** Early neurological deterioration occurs frequently after subarachnoid haemorrhage (SAH). The impact on hospital course and outcome remains poorly defined.

**Methods** We identified risk factors for worsening on the Hunt–Hess grading scale within the first 24 h after admission in 609 consecutively admitted aneurysmal SAH patients. Admission risk factors and the impact of early worsening on outcome was evaluated using multivariable analysis adjusting for age, gender, admission clinical grade, admission year and procedure type. Outcome was evaluated at 12 months using the modified Rankin Scale (mRS).

**Results** 211 patients worsened within the first 24 h of admission (35%). In a multivariate adjusted model, early worsening was associated with older age (OR 1.02, 95% CI 1.001 to 1.03;  $p=0.04$ ), the presence of intracerebral haematoma on initial CT scan (OR 2.0, 95% CI 1.2 to 3.5;  $p=0.01$ ) and higher SAH and intraventricular haemorrhage sum scores (OR 1.05, 95% CI 1.03 to 1.08 and 1.1, 95% CI 1.01 to 1.2;  $p<0.001$  and 0.03, respectively). Early worsening was associated with more hospital complications and prolonged length of hospital stay and was an independent predictor of death (OR 12.1, 95% CI 5.7 to 26.1;  $p<0.001$ ) and death or moderate to severe disability (mRS 4–6, OR 8.4, 95% CI 4.9 to 14.5;  $p=0.01$ ) at 1 year.

**Conclusions** Early worsening after SAH occurs in 35% of patients, is predicted by clot burden and is associated with mortality and poor functional outcome at 1 year.

the impact of early worsening on hospital course and outcome received little attention as a prognostic variable after SAH. In this study we sought to identify predictors for early worsening after SAH and to determine the impact of worsening on outcome.

### METHODS

#### Patient population and clinical management

All SAH patients admitted to the Neurological Intensive Care Unit of Columbia University Medical Center between July 1996 and May 2009 were offered enrolment in the Columbia University SAH Outcomes Project ( $n=1227$ ). Consent rate was 98%. The study was approved by the hospital's institutional review board, and in all cases written informed consent was obtained from the patient or a surrogate. The diagnosis of SAH was established by admission CT scan or by xanthochromia of the CSF if CT was not diagnostic. Patients with SAH due to trauma, arteriovenous malformation, vasculitis or other structural lesions ( $n=242$ ), as well as those aged  $<18$  years ( $n=6$ ) or admitted  $>24$  h after SAH onset ( $n=237$ ) and those without recorded Hunt–Hess grades on admission and worst Hunt–Hess grade within the first 24 h ( $n=24$ ) were excluded. Additionally, admission Hunt–Hess grade V patients were not included in the final analysis due to inability of further deterioration ( $n=109$ ). Clinical management according to guidelines set forth by the American Heart Association has been described in detail previously.<sup>3,4,11</sup> We record the day of aneurysmal SAH as 'day 0' in our database.

### BACKGROUND

Subarachnoid haemorrhage (SAH) is associated with a high mortality and morbidity.<sup>1</sup> The detrimental effect of medical complications in the first 2 weeks after haemorrhage on long term outcome has been extensively studied.<sup>2–5</sup> Additional determinants of poor outcome after SAH include age, neurological state at presentation and large aneurysm size.<sup>1</sup> After the initial neuronal damage caused by the haemorrhage, neurological decline is often observed. Clinical worsening may occur early (within the first 24 h of admission) or late in the course of the disease. Several factors have been associated with clinical deterioration, including aneurysm rebleeding, hydrocephalus, delayed cerebral ischaemia from vasospasm, and seizures.<sup>4,6–10</sup> However, admission variables predicting early neurological decline have not been evaluated, and

### Clinical and radiographic variables, and hospital complications

We recorded baseline demographic data, social and past medical history, clinical features at SAH onset and admission CT scan, as described previously.<sup>3,4,12,13</sup> Neurological and general medical condition on admission was evaluated with the Hunt–Hess scale<sup>12</sup> and the physiological subscore of the Acute Physiology and Chronic Health Evaluation (APACHE)-2 scale.<sup>11</sup> Hunt–Hess grades on admission and at 24 h were evaluated by the treating neurointensivist (JC, NB, KL, SAM) and recorded. Hospital complications were prospectively recorded according to standardised definitions, including fever (body temperature  $\geq 38.3^{\circ}\text{C}$ ), anaemia treated with blood transfusion (haemoglobin  $<9.0$  g/l), aneurysm rebleeding, brainstem herniation, cerebral infarction (from any cause),



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hydrocephalus treated with CSF diversion, hyperglycaemia (blood glucose >11 mmol/l), hyponatraemia (serum sodium  $\leq$ 130 mmol/l), hypotension (systolic blood pressure <100 mm Hg) requiring pressors, sepsis, pneumonia, pulmonary oedema, seizures and delayed cerebral ischaemia (delayed neurological deterioration, cerebral infarction or both) due to vasospasm.<sup>2 14 15</sup> The Bicaudate Index was used as an estimated measure for the development of hydrocephalus.

### Early neurological deterioration

In every patient, admission Hunt–Hess grade and the worst Hunt–Hess grade within the first 24 h of admission were recorded. Early neurological deterioration was defined as any increase in Hunt–Hess scale within the first 24 h of admission, with grades I and II combined as a single group of good grade patients. Procedure or sedation related deterioration was not considered as ‘early neurological deterioration’. The second evaluation was done ‘sedation free’ so as to minimise the effect of sedation. If sedation was considered the culprit, then a higher score was not assigned. External ventricular drain (EVD) placement was immediately performed in symptomatic patients, even before aneurysm repair. In general, EVD was in place by the time of the second score. In patients with early neurological deterioration, hydrocephalus requiring EVD placement was performed in 27% (admission Hunt–Hess grades 1 and 2, n=24/90), 61% (admission Hunt–Hess grade 3, n=42/69) and 81% (Hunt–Hess grade 4, n=42/52). Predictors for early neurological deterioration included only variables obtained on admission (demographics, past medical history, neurological and clinical examination, laboratory analyses and radiographic findings).

### Outcome variables

Survival and functional outcomes were assessed at discharge and at 3 and 12 months, using the modified Rankin Scale (mRS).<sup>16</sup> Poor outcome was defined as death or moderate to severe disability (mRS 4–6) at 12 months. If a 12 month mRS was not performed, day 14 (or discharge) or 3 month evaluation was carried forward.

### Statistical analysis

All statistical analyses were performed using SPSS 18 software (SPSS Inc, Chicago, Illinois, USA). Significance was judged at  $p < 0.05$ . Candidate predictor variables for worsening and mortality were identified by  $\chi^2$  or Fisher exact tests for categorical variables and the Mann–Whitney U or two tailed t tests for continuous variables (table 1). Normality was assessed using the Kolmogorov–Smirnov test. Among similar variables that were highly intercorrelated (ie, clinical scales), only the variable with the highest OR and smallest p value in the binary logistic regression analysis was used as a candidate variable in the final multivariate model. Independent predictors of early worsening, death at 12 months and death or severe disability at 12 months were identified with backward stepwise multiple logistic regression analysis. Factors that occurred at a frequency of <5% were excluded from the final model. To determine the relative contributions of the individual predictors, we used Bayesian information criterion and Akaike’s information criterion of the entire model after individual removal of each significant predictor. Tests for interaction were performed for all variables entered into the multivariable models. When significant two way interactions were identified, we reanalysed the predictive value of each factor after stratifying the analysis between the two levels of the other factor.

**Table 1** Admission factors in relation to neurological deterioration in the first 24 h (n=609)

	Worse (n=211)	Stable (n=398)	p Value
<b>Demographics</b>			
Age (years)	57 (16)	52 (13)	0.001
Female	154 (73)	297 (75)	0.6
Body mass index (kg/m <sup>2</sup> )	27 (6)	27 (7)	0.9
White ethnicity	99 (47)	180 (45)	0.7
<b>Social and past medical history</b>			
Hypertension	118 (56)	175 (43)	0.004
Diabetes mellitus	17 (8)	28 (7)	0.3
Previous stroke	7 (3)	7 (2)	0.2
<b>Admission neurological and clinical findings</b>			
Hunt–Hess grade	3 (2–3)	3 (1–3)	0.3
1 and 2, alert and oriented	90 (43)	179 (45)	
3, lethargic	69 (33)	137 (34)	
4, stuporous	52 (25)	82 (21)	
Loss of consciousness	92 (44)	134 (34)	0.01
APACHE-2 physiological subscore*	6 (4–9)	5 (3–8)	<0.001
Body temperature (°C)	98 (97–99)	98 (97–99)	0.8
Systolic blood pressure (mm Hg)	160 (138–180)	156 (133–180)	0.2
Heart rate (bpm)	82 (69–96)	80 (68–90)	0.3
Respiratory rate (/min)	18 (16–20)	18 (16–20)	0.1
Serum sodium (mmol/l)	139 (136–140)	138 (136–140)	0.9
Serum glucose (mmol/l)	146 (126–178)	137 (118–166)	0.003
White blood cell count ( $\times 10^9/l$ )	11.6 (8.8–14.5)	10.8 (8.3–13.7)	0.08
Troponin ( $\mu g/l$ )†	0.2 (0.02–0.5)	0.1 (0.02–0.3)	0.4
<b>Admission radiographic findings</b>			
Modified Fisher scale	3 (2–4)	3 (1–3)	<0.001
0, no blood	1 (1)	12 (3)	
1, focal or diffuse thin SAH	42 (20)	124 (32)	
2, focal or diffuse thin SAH	16 (8)	29 (7)	
with bilateral IVH			
3, focal or diffuse thick SAH	95 (45)	162 (41)	
4, focal or diffuse thick SAH	57 (27)	71 (18)	
with bilateral IVH			
SAH sum score*	19 (14–24)	15 (10–21)	<0.001
IVH sum score*	2 (0–4)	1 (0–3)	0.005
Bicaudate Index (mm)	0.17 (0.13–0.22)	0.16 (0.12–0.20)	0.004
Haematoma	42 (20)	43 (11)	0.003
Vasospasm on admission angiogram	11 (5)	18 (5)	0.7
Aneurysm size >10 mm	54 (26)	92 (23)	0.4

Values are presented as mean (SD), median (IQR) or number (%).

\*APACHE-2 physiological subscore is the sum of four physiological variables:

arterio-alveolar gradient >125 mm Hg=3, HCO<sub>3</sub> <20 mmol/l=2, glucose 9.9 mmol/l=2 and mean arterial pressure <70 or >130 mm Hg=1 (range 0–8); SAH sum score grades the amount of blood in 10 basal cisterns and fissures (0=no SAH, 1=small SAH, 2=moderate SAH, 3=completely filled with SAH) by adding each of the 10 individual cistern scores (range 0–30); IVH sum score grades the amount of blood in the right and left lateral, third and fourth ventricle (0=no blood, 1=sedimentation, 2=partly filled, 3=completely filled) by adding each of the four individual ventricle scores (range 0–12).

†Missing variables in 45%.

APACHE, Acute Physiology and Chronic Health Evaluation, ICH, intracerebral haemorrhage; IVH, intraventricular haemorrhage; SAH, subarachnoid haemorrhage.

## RESULTS

### Frequency of early neurological deterioration

Of the 609 patients eligible for analysis, early worsening occurred in 35% of patients (n=211), equally distributed in patients where aneurysm was coiled (34%) and clipped (35%). Aneurysm repair was performed on day 1 of admission (median, IQR 1–1). Early worsening occurred by one (58%; to

**Table 2** Multivariate analysis predicting neurological deterioration in the first 24 h\*

Variable	OR	95% CI	p Value
Age	1.02	1.001 to 1.03	0.04
Intracerebral haematoma on initial CT	2.0	1.2 to 3.5	0.01
SAH sum score†	1.05	1.03 to 1.08	<0.001
IVH sum score†	1.1	1.01 to 1.18	0.03

\*Adjusted for gender, admission Hunt–Hess grade, admission year and surgical/endovascular treatment.

†SAH and IVH sum scores are as described in the legend to table 1.

IVH, intraventricular haemorrhage; SAH, subarachnoid haemorrhage.

Hunt–Hess grade 3, n=63; to Hunt–Hess grade 4, n=42; to Hunt–Hess grade 5, n=52), two (34%; to Hunt–Hess grade 4, n=17; to Hunt–Hess grade 5, n=27) or three (8%; to Hunt–Hess grade 5, n=10) Hunt–Hess categories.

### Predictors of early neurological deterioration

Of the clinical and radiographic variables associated with worsening in the univariate analysis (table 1), older age, intracerebral haematoma on initial CT scan, higher SAH sum and intraventricular haemorrhage sum scores were independent predictors of worsening within the first 24 h (table 2), after adjusting for admission Hunt–Hess grade, gender, admission year and procedure type (surgical/endovascular treatment of ruptured aneurysms). No interactions were found between these predictors in this final model.

### Hospital complications

The rate of hospital complications was higher in patients with early neurological deterioration, as shown in table 3.

**Table 3** Hospital complications and outcome in relation to neurological deterioration in the first 24 h (n=609)

	Worse (n=211)	Stable (n=398)	p Value
Fever >38.3°C	153 (73)	184 (46)	<0.001
Anaemia treated with blood transfusion	114 (54)	115 (29)	<0.001
Aneurysm rebleeding	35 (17)	15 (4)	<0.001
Herniation	52 (25)	18 (5)	<0.001
Hydrocephalus treated with CSF diversion	108 (51)	104 (26)	<0.001
Hyperglycaemia (>11 mmol/l)	124 (59)	171 (43)	<0.001
Hyponatraemia (<130 mmol/l)	36 (17)	59 (15)	0.477
Hypotension requiring vasopressors	67 (32)	65 (16)	<0.001
Pneumonia	82 (39)	58 (15)	<0.001
Pulmonary oedema	68 (32)	44 (11)	<0.001
Seizure	25 (12)	15 (4)	<0.001
Sepsis	41 (19)	31 (8)	<0.001
Delayed cerebral ischaemia	73 (35)	61 (15)	<0.001
ICU LOS	13 (9–19)	9 (7–12)	<0.001
Hospital LOS	20 (13–31)	13 (11–19)	<0.001

Values are presented as median (IQR) or number (%).

$\chi^2$ , Fisher exact tests or Mann–Whitney U or two tailed t tests were used as appropriate.

ICU, intensive care unit; LOS, length of stay.

### Twelve month outcome

Twelve month outcome data are presented in figure 1, including 184 patients (30%) where mRS was carried forward. Mortality was higher in patients with early neurological deterioration (18%, n=38, compared with 1%, n=2, at 14 days, and 28%, n=60, compared with 3%, n=13, at 12 months, p<0.001, respectively). Good recovery at 1 year (mRS 0–3) was observed in 52% of patients with early neurological deterioration (n=110) compared with 88% without neurological decline in the first 24 h of admission (n=351, p<0.001). Of the variables associated with mortality and severe disability and mortality in univariate analysis, age, admission Hunt–Hess grade, inhospital hyperglycaemia and early neurological deterioration were independently associated with 12 month outcomes (variables that were forced in the model were gender, admission year and surgical/endovascular treatment) (table 4).

### DISCUSSION

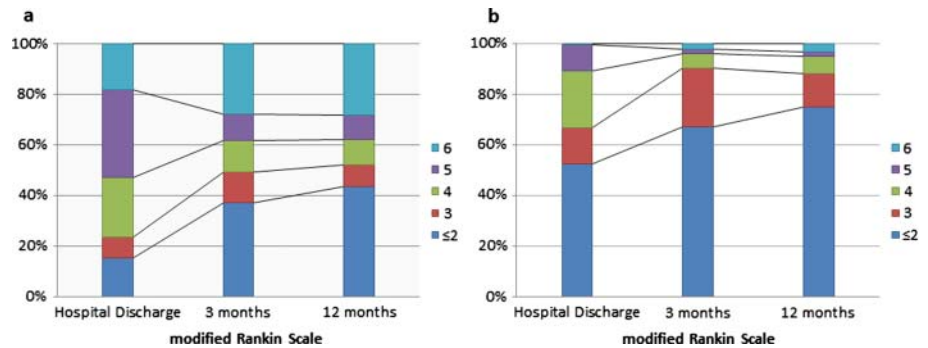
We found that early neurological deterioration after SAH is a strong predictor of death and poor functional recovery at 1 year. Older age and overall clot burden on admission predicted clinical worsening.

The most novel finding in this study is that the initial haemorrhage load is an independent predictor for early neurological deterioration after SAH, regardless of whether the blood is intraventricular, intracerebral or in the subarachnoid space. The association of clot burden and early neurological deterioration may be explained by the evolving mass effect with intracerebral haemorrhage or through the development of obstructive hydrocephalus in patients with intraventricular bleeding.<sup>17</sup> Although we did not find an association between the Bicaudate Index on admission and neurological deterioration, patients may have developed hydrocephalus thereafter.

One can only speculate why the amount of subarachnoid blood in direct contact with the brain predicts early neurological deterioration. It may be that the toxicity of blood drives early metabolic and electrical failure of brain cells. This concept of neurohaemoinflammation is based on mechanical, biochemical and molecular changes, eventually leading to oedema, neurovascular uncoupling, apoptosis and cell death.<sup>18 19</sup> Carefully designed studies using multimodal neuromonitoring techniques (microdialysis, brain tissue oxygen and EEG monitoring) or neuroimaging modalities (MR, positron emission tomography, single photon emission computed tomography) may capture these early pathophysiological changes in brain metabolism and physiology.

Given the observed association between clot burden and early worsening, another target for intervention may be found in decreasing haemorrhage related energy demand of the acutely injured brain after poor grade SAH by pharmacological measures or hypothermia. Although intraoperative hypothermia does not improve outcome during aneurysm clipping,<sup>20 21</sup> early and more prolonged hypothermia may be beneficial as a means of reducing cerebral energy demand or the tissue inflammatory response. Another strategy to minimise the harmful effects of subarachnoid and intraventricular blood might include cisternal or ventricular lavage, kinetic therapy or other methods for promoting early blood clearance.<sup>22</sup> Early evacuation of packed intraventricular haemorrhage in poor grade SAH patients, however, did not show a favourable outcome.<sup>23</sup> There is some evidence that lumbar drainage of CSF decreases symptomatic vasospasm and improves outcome after SAH<sup>24</sup>

**Figure 1** Outcome of patients with (A, n=211) and without (B n=398) early neurological deterioration using the modified Rankin Scale (mRS) at hospital discharge, and at 3 months and 12 months after subarachnoid haemorrhage. Percentages of subjects in different mRS categories are shown, with grades 0–2 combined as a single group of patients. This figure is only reproduced in colour in the online version.



but larger randomised trials are needed to support this intervention.

The prognostic value of early worsening for poor outcome at 12 months is similar to that of previously identified risk factors, such as age, admission Hunt–Hess, rebleeding and aneurysm size. The strong association between worsening and various hospital complications in our study may account in part for the association with poor outcome. Haemorrhage load and the presence of intraventricular blood after SAH have been associated with in-hospital complications and increased mortality.<sup>3 6 25</sup> The most common hospital complication among patients with early neurological deterioration was fever (72%), which is a frequent epiphenomenon in neurocritical care patients,<sup>26</sup> and is associated with neurological deterioration and poor outcome.<sup>2 7 27 28</sup> Prevention of fever after SAH is a widely accepted management strategy and may improve outcome.<sup>29</sup>

Fifty-five per cent of patients with early worsening developed hyperglycaemia during hospitalisation. Prevention of hyperglycaemia has previously been shown to improve outcome in surgical and medical patients,<sup>30 31</sup> but more recent trials have challenged these findings,<sup>32</sup> leading to controversy regarding the optimal range of serum glucose in critical care.<sup>32 33</sup> In acutely brain injured patients, the detrimental effect of hyperglycaemia on hospital course and functional outcome has been well studied<sup>5 34 35</sup> but tight glycaemic control (4.4–6.2 mmol/l) has recently been associated with brain metabolic distress,<sup>36</sup> as brain tissue glucose is primarily regulated by systemic supply.<sup>37</sup> Prolonged cerebral tissue hypoglycaemia is predictive for poor

outcome,<sup>38 39</sup> therefore arguing for a less restrictive target for systemic glycaemic control in acutely brain injured patients.<sup>40</sup>

Several potential weaknesses of this study deserve mention. The single centre design of our study limits the generalisability of our results. The major limitation of this study is that other factors, which potentially cause early neurological deterioration (seizures, stunned myocardium, fever, etc.) were not investigated as these data were not recorded in a time locked way in our database. Furthermore, our data provide no information on early worsening in Hunt–Hess grade V patients, as they were not included in our analysis. Patients may deteriorate prior to hospital admission and after the first 24 h, and our study provides no data on these events. Finally, we analysed only admission predictors of neurological worsening. Due to the complex nature of neurological injury in SAH, we found it impossible to reliably identify specific complications, such as intracranial hypertension, obstructive hydrocephalus, brainstem herniation, seizures, rebleeding or acute cerebral infarctions as the primary cause of early worsening in individual patients. Although we record these complications in our database, we also do not have information regarding the timing of these events. Moreover, the exact hour of SAH bleeding and the exact time of neurological deterioration after admission was not recorded prospectively, which could also have influenced our results. If a 12 month mRS was not performed, the day 14 (or discharge) or 3 month evaluation was carried forward. The model predicting 1 year outcome was recalculated without patients with missing 12 month evaluations (30%) and did not show a significant change in variables.

**Table 4** Predictors of mortality or severe disability and of mortality 12 months after subarachnoid haemorrhage\*

Variable	Dead or severely disabled†			Dead		
	OR	95% CI	p Value	OR	95% CI	p Value
Age	1.05	1.03 to 1.07	<0.001	1.05	1.02 to 1.07	<0.001
Admission Hunt–Hess	2.6	1.9 to 3.4	<0.001	2.3	1.6 to 3.3	<0.001
Hyperglycaemia (>11 mmol/l)‡	2.2	1.2 to 4.1	<0.001			
Neurological deterioration in first 24 h	8.4	4.9 to 14.5	0.01	12.1	5.7 to 26.1	<0.001

\*Adjusted for gender, admission year and surgical/endovascular treatment.

†Defined as modified Rankin Scale >3.

‡Hyperglycaemia (≥11 mmol/l) at any point during hospitalisation.

## CONCLUSIONS

In conclusion, our findings indicate that early neurological deterioration is an important predictor of poor outcome after SAH. Carefully designed prospective studies are needed to understand the pathophysiology of this phenomenon. Medical therapies aimed at preventing early deterioration after SAH may improve outcome.

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**Competing interests** None.

**Ethics approval** The study was approved by the institutional review board of Columbia University New York.

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