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Warning headache correlates survival rate in aneurysmal subarachnoid hemorrhage



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ABSTRACT

Background: Severe headaches, projectile vomiting, focal neurological deficits and early onset seizure are regarded as early warning symptoms of subarachnoid hemorrhage (SAH). Earlier diagnosis based on such warning symptoms theoretically would improve the clinical prognosis. However, it is still not clear whether the prognosis is correlated with early warning symptoms. Here, we reviewed warning symptoms and other predictive factors in the emergency room (ER) setting and examined their correlations with mortality.

Methods: Ninety saccular aneurysmal SAH cases were reviewed in a single medical center between January 2011 and December 2013. We examined differences in mortality rate related to warning symptoms, SAH scales, onset-to-ER time, hydrocephalus, and aneurysm size, location, and complexity. Logistic regression analyses were performed to determine the correlations of warning symptoms and other predictive factors with mortality. Receiver operating characteristic (ROC) curve analysis was used to calculate the area the under curve (AUC) of SAH mortality prediction tools.

Results: Warning headache, projectile vomiting, the Hunt and Hess scale, Fisher scale, World Federation of Neurological Surgeons (WFNS) grading scale, and modified WFNS (m-WFNS) scale, body mass index, aneurysm complexity and hydrocephalus were significantly different between the survivors and the decedents. The warning headache and WFNS grade were strongly correlated with mortality. The rate of prognostic prediction improved from 90.4% to 94.6% when warning headache was additionally evaluated.

Conclusions: With growing healthcare costs and recognition of the value of palliative care, early identification via warning headache and a detailed clinical history review is necessary for cases of aSAH.

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At a glance commentary

Scientific background on the subject

Explosive headache is regarded as early warning symptoms of aneurysmal subarachnoid hemorrhage (aSAH). It is still not clear whether the prognosis is correlated with warning symptoms. In this study, we reviewed warning symptoms and other predictive factors in the emergency room (ER) setting and examined their correlations with mortality.

What this study adds to the field

With growing healthcare costs, it is important to survey markers of survival in aSAH patients. The warning headache and the WFNS can be markers of survival in the ER. Aggressive management in aSAH patients with warning headache and lower WFNS scales should be encouraged because of a higher survival rate.

Aneurysmal subarachnoid hemorrhage (aSAH) is life threatening, especially during middle age [1-3]. Several grading systems have been developed for the initial assessment of patients with aSAH, including the Hunt and Hess scale [4], Fisher scale [5], World Federation of Neurological Surgeons (WFNS) grading scale for subarachnoid hemorrhage [6], and modified WFNS (m-WFNS) scale [7]. The Hunt and Hess scale is associated with interobserver variability based on the conventional classifications of impaired consciousness, such as "drowsiness," "stupor," or "deep coma" [8,9]. Despite its widespread use, the Fisher scale has a limited ability to predict outcomes [10,11]. The early mortality, vegetative state, and length of neurocritical care remained high in aSAH patients with a poor WFNS grade [12,13]. However, a good outcome was reported in 26–53% of WFNS grade IV-V patients when treated aggressively [12–14]. The m-WFNS scale is easier to use than is the WFNS

scale with assignment of Glasgow Coma Scale (GCS) score 14 to grade II and GCS score 13 to grade III, but its external and internal validities remain unknown [7].

Sudden and severe headaches, projectile vomiting, focal neurological deficits and early onset seizure are regarded as warning symptoms of aSAH [15]. Earlier diagnosis based on warning symptoms may improve the clinical prognosis. However, Behrouz et al. [16] reported that initial focal neurological deficit in aSAH is an independent predictor of poor outcome [16]. It is still not clear whether the prognosis is correlated with warning symptoms. With increasing healthcare costs and recognition of the value of palliative care, prognostic prediction before management is becoming increasingly relevant. Therefore, we reviewed clinical warning symptoms and other available predictive factors in the emergency room (ER) and examined their correlations with mortality in aSAH.

Methods

Study population

We retrospectively evaluated 108 patients with aSAH between January 2011 and December 2013 in one medical center. The inclusion criteria were patients with (1) saccular aSAH and (2) available computed tomography angiography, magnetic resonance angiography, or digital subtraction angiography images documenting aneurysm characteristics. Exclusion criteria were (1) infective, traumatic, dissecting, or fusiform aneurysms, (2) flow-related aneurysms associated with arteriovenous malformations, and (3) no available aneurysm size, location, or complexity data. Considering different underlying etiology and short-term outcome, we excluded 13 cases with dissecting or fusiform aneurysms [17,18]. We excluded 5 cases without imaging study data. Finally, we enrolled 90 patients in the present study.

This study was approved by the institutional review board. The requirement for informed consent was waived, because this was a retrospective medical and imaging review, and no additional interventions were performed.

Table 1 Demographic data comparisons by mortality.				
Alive ($n = 70$)	Dead ($n = 20$)	p-value		
56.00 (47.75, 64.00)	59.50 (48.00, 75.00)	0.166		
24.00 (34.29)	8.00 (40.00)	0.638		
25.20 (22.25, 27.72)	22.42 (21.05, 25.77)	0.034*		
5.00 (7.14)	3.00 (15.00)	0.369		
4.00 (5.71)	3.00 (15.00)	0.181		
42.00 (60.00)	10.00 (50.00)	0.425		
6.00 (8.57)	3.00 (15.00)	0.410		
6.00 (8.57)	1.00 (5.00)	1.000		
8.00 (11.43)	1.00 (5.00)	0.677		
2.00 (2.86)	1.00 (5.00)	0.534		
273.00 (84.00, 646.00)	165.00 (87.00, 281.00)	0.312		
	Alive (n = 70) $56.00 (47.75, 64.00)$ $24.00 (34.29)$ $25.20 (22.25, 27.72)$ $5.00 (7.14)$ $4.00 (5.71)$ $42.00 (60.00)$ $6.00 (8.57)$ $6.00 (8.57)$ $8.00 (11.43)$ $2.00 (286)$ $273.00 (84.00, 646.00)$	lity.Alive $(n = 70)$ Dead $(n = 20)$ $56.00 (47.75, 64.00)$ $59.50 (48.00, 75.00)$ $24.00 (34.29)$ $8.00 (40.00)$ $25.20 (22.25, 27.72)$ $22.42 (21.05, 25.77)$ $5.00 (7.14)$ $3.00 (15.00)$ $4.00 (5.71)$ $3.00 (15.00)$ $42.00 (60.00)$ $10.00 (50.00)$ $6.00 (8.57)$ $3.00 (15.00)$ $6.00 (8.57)$ $1.00 (5.00)$ $8.00 (11.43)$ $1.00 (5.00)$ $2.00 (2.86)$ $1.00 (5.00)$ $273.00 (84.00, 646.00)$ $165.00 (87.00, 281.00)$		

Data are presented as median (interquartile range, IQR) or n (%).

^a n = 65 in the alive group, n = 15 in the dead group.

^b n = 68 in the alive group, n = 20 in the dead group.

Baseline characteristics and demographic assessment

We collected baseline characteristics and demographic information, such as age, gender, body mass index (BMI), personal history of cigarette smoking, alcohol consumption, past history of hypertension, diabetes mellitus (DM), heart disease, malignancy, and ischemic or hemorrhagic stroke, time interval between onset and ER arrival (Table 1). We reviewed initial clinical warning symptoms related to aneurysms, such as severe explosive headache, projectile vomiting, ocular symptoms, slurred speech, limb weakness, early-onset seizure, or transient loss of consciousness [15]. Imaging and procedure data were collected for aneurysm size, location, complexity, and management methods. Aneurysms with the following features were defined as complex aneurysms: wide neck (greater than the diameter of the parent artery), intraaneurysm thrombus, proximal vessel tortuosity/stenosis, and branch artery incorporated into the neck or aneurysm sac [19]. We collected data on the patients' initial Hunt and Hess scale, Fisher scale, WFNS scale, and m-WFNS scale scores; presentation of hydrocephalus; intervention methods; and whether they survived or died.

Statistical analysis

Continuous variables are reported as means (standard deviation) or medians (interquartile range) as appropriate. Categorical variables are reported as proportions. Continuous variables were compared by the Mann–Whitney U test, while categorical variables were compared by the chi-square test and Fisher's exact test. We examined the relationships between mortality rate and aSAH patient baseline conditions, initial aSAH scales, warning symptoms, imaging findings of hydrocephalus, and aneurysm characteristics before treatment. Logistic regression analyses were performed to determine the correlations between predictive factors and mortality. Receiver operating characteristic (ROC) curve analysis was used to calculate the area the under curve (AUC) to evaluate predictive models. Significance was set at P < 0.05, and all P-values were two-sided. All statistical analyses were performed using SPSS, version 24 (SPSS Inc.).

Results

Among the 90 patients, the mean age was 56.84 ± 13.15 years (range: 26-91 years) and 32 (35.56%) were men. There were no significant differences in baseline characteristics, including age, gender, smoking habits, alcohol consumption, medical history of hypertension, DM, heart disease, malignancy, stroke, and onset-to-hospital time between the survivors and the decedents. Likewise, there were no significant differences between the two groups in terms of aneurysm size and location. Lower BMI, more hydrocephalus and more complex aneurysms were found in the decedents (Table 2). Total 73 patients received intervention (29 clippings and 44 embolization cases) and 17 cases received conservative management. More clippings were performed in the MCA aneurysm cases for easy surgical access, higher complete obliteration rate and lower recurrence rate [20,21]. There was no significant

Table 2 Comparison of aneurysm data and hydrocephalus condition by mortality.				
	Alive (n = 70)	Dead (n = 20)		

p-

			value
Aneurysm max size mm, median (IQR)	5.00 (3.58, 7.00)	7.00 (3.63, 11.53)	0.135
Aneurysm locations			
AComA, n (%)	32.00 (45.71)	8.00 (40.00)	0.650
PComA, n (%)	10.00 (14.29)	2.00 (10.00)	1.000
MCA, n (%)	14.00 (20.00)	3.00 (15.00)	0.754
ICA, n (%)	6.00 (8.57)	5.00 (25.00)	0.062
VA/BA, n (%)	8.00 (11.43)	2.00 (10.00)	1.000
Complex aneurysm, n (%)	32.00 (45.71)	17.00 (85.00)	0.002*
Hydrocephalus n (%)	47.00 (67.14)	18.00 (90.00)	0.044*
EVD, n (%)	44.00 (62.86)	8.00 (40.00)	0.068
Data are presented as median (interquartile range, IQR) or n (%).			

difference in managing strategy for aneurysms of other locations. Moreover, the survival rate got no significant difference between the clipping and the embolization groups (Table 3).

Higher median scores of the Hunt and Hess, Fisher, WFNS, m-WFNS were found in the decedents. The warning symptoms included severe explosive headache (54.44%), projectile vomiting (22.22%), and focal neurological deficits (dizziness, 13.33%; transient consciousness loss or early-onset seizure, 10.00%; aphasia, 2.22%; limb weakness, 3.33%; slurred speech, 3.33%; and ocular symptoms, 2.22%). More explosive headaches and projectile vomiting were reported in the survivor group. The median onset-to-hospital time was not significantly different between patients with and without warning symptoms of headache or vomiting (313 min vs. 198 min, P = 0.501). Patients with headache or projectile vomiting had lower grade SAH scales, such as the Hunt and Hess, WFNS and m-WFNS (P < 0.001). Early-onset seizure and focal neurological deficits, such as dizziness, aphasia, limb weakness, showed no marked differences between the survivors and the decedents (Table 4).

We performed univariate logistic regression and backward Wald stepwise logistic regression to examine the correlations of mortality with Hunt and Hess, Fisher, WFNS, and m-WFNS scale grades, warning symptoms of headache and vomiting, hydrocephalus, BMI and aneurysm complexity (Table 5). The backward Wald stepwise logistic regression revealed correlations of mortality with warning headache (Adjusted odds ratio = 0.060, P = 0.016) and the WFNS grade (Adjusted odds ratio = 7.061, P = 0.005). Patients with early warning headache and lower score of WFNS would be more likely alive. Besides, a new model was constructed with the coefficient of WFNS and

Table 3 Comparison of aneurysm location and survival rate by intervention with clipping and embolization.			
	Clipping (n = 29)	Embolization $(n = 44)$	p value
Acom, n (%)	12 (41.38)	21 (47.73)	0.594
Pcom, n (%)	5 (17.24)	5 (11.36)	0.505
MCA, n (%)	9 (31.03)	5 (11.36)	0.037*
ICA, n (%)	1 (3.45)	6 (13.64)	0.232
VA/BA, n (%)	2 (6.90)	7 (15.91)	0.303
Survival rate, n (%)	29 (100.00)	40 (90.91)	0.147

symptoms by mortality.			
	Alive	Dead	p-
	(n = 70)	(n = 20)	value
Hunt and Hess, median (IQR)	2 (2,4)	4 (4,5)	<0.001*
Fisher scale, median (IQR)	3 (2,4)	4 (4,4)	< 0.001*
WFNS, median (IQR)	2 (1,4)	5 (5,5)	< 0.001*
m-WFNS, median (IQR)	2.5 (1,4)	5 (5,5)	< 0.001*
Warning symptoms			
Headache, n (%)	48.00 (68.57)	1.00 (5.00)	< 0.001*
Vomiting, n (%)	19.00 (27.14)	1.00 (5.00)	0.037*
Dizziness, n (%)	12.00 (17.14)	0.00 (0.00)	0.061
Transient consciousness change	8.00 (11.43)	1.00 (5.00)	0.677
or seizure, n (%)			
Aphasia, n (%)	2.00 (2.86)	0.00 (0.00)	1.000
Limbs weakness, n (%)	2.00 (2.86)	1.00 (5.00)	0.534
Ocular signs, n (%)	2.00 (2.86)	0.00 (0.00)	1.000
Slurred speech, n (%)	3.00 (4.29)	0.00 (0.00)	1.000
Data are presented as median (interquartile range, IQR) or n (%).			

headaches were 1.955 and -2.816. ROC curve analysis assesses the performance of prediction models. Using SPSS, we set the death status of the patient and performed ROC curve analysis to calculate the AUCs of the Hunt and Hess (0.865), Fisher (0.739), WFNS (0.904), m-WFNS (0.903) scale grades and the new model (0.946). The rate of prognostic prediction improved from 90.4% to 94.6% after adding clinical warning symptoms to the analysis.

Discussion

The warning headache showed a good correlation with mortality, which may be related to initial lower SAH scales. The median WFNS scale was lower in patients with warning headache (Grade I vs. grade IV, p < 0.001). The warning headache that occurs at the time of aSAH onset, mostly at occipital locations, reaches maximum severity within minutes and lasts for hours to days [22]. Although warning headache might prompt patients to seek medical help earlier, the median onset-to-ER time got no significant difference between patients with or without headache (336 min and 183 min, p = 0.307). The correlation between

warning headache and survival was not related to earlier detection. Warning headache here included not only "ictal headache" but also "sentinel headache". Sentinel headache occurs days or weeks before SAH. Sentinel headache is believed to cause by aneurysm growth or microscopic aneurysmal rupture [23].

Projectile vomiting was regarded as an early predictor of the outcome of ischemic and hemorrhagic stroke [24]. But the univariate logistic regression did not include projectile vomiting as a predictor of survival in this study. Behrouz et al. [16] reported that an early focal neurological deficit was an independent factor related to poor prognosis. Focal neurological deficits include hemiparesis, hemisensory loss, hemianopia, or aphasia. In this study, focal neurological deficits were not related to mortality statistically. Early-onset seizure in aSAH patients was thought to be an independent predictor of poor outcome [25], but Fung et al. suggested that early-onset seizure was associated with good outcome [26]. Brain herniation with seizure-like tonic movement would be misinterpreted as seizures [23]. The disparity of interpretation might partly explain the outcome discrepancy. In this study, early-onset seizure or changes in transient consciousness showed no obvious differences between the survivors and the decedents.

Considering the economic burden associated with their death, it is important to survey markers of survival in aSAH patients, most of whom are middle-aged [3]. The Hunt and Hess, Fisher, WFNS, and m-WFNS scales are useful tools for classification of aSAH [4-6,10,27]. The m-WFNS scale is simpler than the WFNS, and the AUC was reported to be higher for the former score than for the latter score in patients with a modified Rankin scale (mRS) < 1 at discharge or at 90 days [7]. In this study, the AUC of the m-WFNS scale score was only slightly smaller than that of the WFNS scale score in the decedents (0.903 vs. 0.904, respectively). Patients with higher WFNS/m-WFNS grades seemed to exhibit higher proportions of poor outcomes than those with lower WFNS/m-WFNS grade [7,27]. Rosen and MacDonald [28] attempted to improve the predictive power of WFNS by adding seven clinical and radiological factors, but they found that the scale was too complex. The SAH score, which includes the GCS score, age, and medical comorbidities, showed better predictive power than did the WFNS or Hunt and Hess scales, but the SAH score is not in widespread use [29].

Table 5 Univariate and backward Wald stepwise logistic regression demonstration of the predictive factors and mortality.				
Crude odds ratio	95% confidence interval of crude odds ratio	p-value		
6.528	(2.561, 16.638)	< 0.001*		
6.101	(1.684, 22.098)	0.006*		
7.826	(2.510, 24.395)	< 0.001*		
8.217	(2.661, 25.372)	< 0.001*		
0.024	(0.003, 0.192)	< 0.001*		
0.141	(0.018, 1.129)	0.065		
6.729	(1.808, 25.049)	0.004*		
4.404	(0.941, 20.619)	0.060		
0.843	(0.712, 0.998)	0.047*		
Adjusted odds ratio	95% confidence interval of adjusted odds ratio	p-value		
0.060	(0.006, 0.590)	0.016*		
7.061	(1.810, 27.541)	0.005*		
	Crude odds ratio 6.528 6.101 7.826 8.217 0.024 0.141 6.729 4.404 0.843 Adjusted odds ratio 0.060 7.061	Crude odds ratio 95% confidence interval of crude odds ratio 6.528 (2.561, 16.638) 6.101 (1.684, 22.098) 7.826 (2.510, 24.395) 8.217 (2.661, 25.372) 0.024 (0.003, 0.192) 0.141 (0.018, 1.129) 6.729 (1.808, 25.049) 4.404 (0.941, 20.619) 0.843 (0.712, 0.998) Adjusted odds ratio 95% confidence interval of adjusted odds ratio 0.060 (0.006, 0.590) 7.061 (1.810, 27.541)		

Good prognostic prediction was demonstrated in our study using the WFNS scale (90.4%). The strong correlation between mortality and WFNS grade and inverse warning symptoms of headache resulted in better prediction of prognosis (94.6%). This suggests that prognostic prediction could be improved by adding warning headache along with the WFNS grade in the evaluation. The warning headache and the WFNS can be markers of survival in the ER. Further clarification of warning symptoms is required to facilitate aSAH recognition by emergency services and to improve prognosis. Aggressive management in aSAH patients with warning headache should be encouraged, because it was associated with a higher survival rate in this study.

The present study had several limitations. First, this was a retrospective study and therefore susceptible to selection bias. The warning headache and projectile vomiting were found at higher rates in the survivors than in the patients who died. The frequency of warning symptoms may be underestimated in the decedents. Second, there may be missing data for SAH patients. Patients with mild symptoms might not visit hospitals and patients with atypical symptoms might not been diagnosed. Patients with aSAH may die before transferring to hospitals. Third, this was a cross-sectional study, and longterm follow-up of neurological outcomes was therefore not available. Forth, the number of cases was relatively small. Therefore, further investigations in larger cohorts are required to improve short-term and long-term prognostic prediction in aSAH.

Conclusion

The WFNS scale is a good prognostic prediction tool for mortality in aSAH (90.4%). The rate of prognostic prediction was improved after adding warning headache to the analysis. We suggest that the WFNS grade should be evaluated along with warning headache for better prognostic prediction. Further investigations in large cohorts assessed using both the WFNS scale and warning symptoms are required.

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Conflicts of interest

The authors report no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bj.2019.04.006.

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