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Case study

PHASES score applied to a prospective cohort of aneurysmal subarachnoid hemorrhage patients

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ABSTRACT

The treatment of unruptured intracranial aneurysms remains controversial. The PHASES score was developed to predict the 5-year risk of aneurysm rupture. We have assigned PHASES scores to a cohort of aneurysmal subarachnoid hemorrhage (aSAH) patients to assess the distribution of scores and its ability to predict outcome. In this study, the PHASES score was applied to a prospective cohort of aSAH patients that were enrolled in the Cerebral Aneurysm Renin Angiotensin System (CARAS) study. The CARAS study enrolled patients from two academic institutions in the United States from 2012 to 2015. Univariable and multivariable analyses were performed to identify factors predictive of outcome at last follow up. One hundred and forty-nine aSAH patients were included with a mean age of 54.9 ± 12.5 years. Most ruptured aneurysms were <7 mm (62.4%) and located in the anterior circulation (80.5%). Favorable functional outcome (mRS 0–2) at last follow up was achieved in 61.7% of patients. PHASES scores ranged from 0 to 16 with a median of 5; the majority of patients had a score of 4 (20.1%) or 5 (32.2%). Multivariable modeling identified higher PHASES scores (OR 1.235, CI 1.016–1.501, p = 0.034) and higher Hunt and Hess grades (OR 2.224, CI 1.353–3.655, p = 0.002) as independent predictors of poor functional outcome (mRS 3–6) at last follow up. The majority of aSAH patients present with low (≤5) PHASES scores. Elevated PHASES scores are independently associated with poor functional outcome in patients with aSAH.

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1. Introduction

The prevalence of unruptured intracranial aneurysms (UIA) is estimated at 3% of the adult population [1]. Rupture of an intradural intracranial aneurysm results in subarachnoid hemorrhage, a unique form of hemorrhagic stroke associated with high morbidity and mortality rates. Roughly a quarter of aneurysmal subarachnoid hemorrhage (aSAH) patients will die with half of the survivors suffering a permanent neurological deficit [2]. Mitigating the risk of aneurysm rupture can be accomplished through modification of risk factors (i.e. blood pressure control, smoking cessation) and aneurysm treatment [3–5]. Endovascular and surgical treatment of UIAs are associated with rates of unfavorable outcomes, including death, of 4.8 and 6.7%, respectively [6,7]. The risk of treatment must be balanced against the risk of aneurysm rupture over the remaining life of the patient.

The PHASES score was developed to predict a patient's risk of aneurysm rupture based on 6 routinely assessed patient and aneurysm characteristics [8]. Despite methodological concerns regarding the development of the PHASES score [9], it is commonly

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used, in whole or in part, to guide clinical decision making. It is widely recognized that despite reassuring "natural history" data [10,11], the majority of ruptured aneurysms are small anterior circulation aneurysms that likely would have received low PHASES scores [12,13].

We have assigned PHASES scores to a prospective cohort of aSAH patients in the United States to assess the distribution of scores and its ability to predict functional outcome.

2. Materials and methods

The PHASES score was applied to a prospective cohort of aSAH patients with the concept that, if the PHASES score was predictive, there should be a preponderance of high scores among the population with rupture. All patients were obtained from the Cerebral Aneurysm Renin-Angiotensin System (CARAS) study that was performed at 2 academic institutions in the United States from September 2012 to January 2015 with a primary objective of evaluating the role of common renin-angiotensin system genetic polymorphisms in aSAH [14,15].

The study was approved by the Institutional Review Board.

2.1. Patients

Consecutive adult patients presenting with aSAH were screened for inclusion. The diagnosis of aSAH was established on the basis of the admission CT scan or xanthochromia in cerebrospinal fluid. A ruptured aneurysm as the source of hemorrhage was confirmed by CT angiography or digital subtraction angiography. Exclusion criteria included: age under 19 years, an associated genetic predisposition to cerebral aneurysm formation (i.e. polycystic kidney disease, Turner syndrome, Noonan syndrome, Ehlers-Danlos syndrome Type 4, Marfan syndrome, or Neurofibrobromatosis Type 1), and systemic disease (i.e. congestive heart failure or cirrhosis) that could interfere with renin-angiotensin system activity. Patients were enrolled within 72 h of hospital admission. It is notable that exclusion criteria did not overlap with any variable included in the PHASES score. A flowchart of participant enrollment has previously been published [14].

Clinical and radiographic data were collected prospectively by two authors (PMF and CJG). Data points included race, past medical history to include hypertension and previous history of aSAH, age, aneurysm size, and aneurysm location, i.e., data points included in the PHASES score. The PHASES score assigns points in 6 categories *P*opulation (0–5), *H*ypertension (0–1), *A*ge (0–1), *S*ize of aneurysm (0–10), *E*arlier SAH from another aneurysm (0–1), and *S*ite of aneurysm (0–4) with a total score ranging from 0 to 22. Only data present on admission were used for univariable and multivariable analysis for predictors of outcome.

2.2. General management

Patients presenting with aSAH were treated in accordance with contemporary standards of care in the United States, consisting of intensive care unit (ICU) monitoring, treatment of hydrocephalus, early (<48 h) intervention for aneurysm treatment, oral nimodipine, maintenance of euvolemia, compression stockings, and sequential compression devices. Symptomatic vasospasm as indicated by focal (i.e. hemiparesis, aphasia) or global (i.e. decreased level of consciousness) neurologic decline in the setting of non-invasive (i.e. transcranial Doppler ultrasonography, computed tomography angiography) or angiographic evidence of vasospasm was treated with hyperdynamic therapy as first-line therapy. Hyperdynamic therapy includes strict avoidance of hypovolemia with a systolic blood pressure goal of more than 160 mm Hg, accomplished with either permissive hypertension or vasopressor therapy. Patients with symptomatic vasospasm refractory to medical management were treated in the endovascular suite with intra-arterial therapy at the discretion of the neurointerventionalist. Following discharge from the ICU, patients were transferred to a neurological step-down unit and a neurosurgical ward with specialty training in patients with aSAH.

2.3. Patient outcome

Outcome measures included mortality and functional outcome at last follow up using the modified Rankin Scale (mRS). Poor outcome was defined as death or moderate disability (mRS Score 3–6). Functional outcome was assessed either in the clinic or via telephone interview with the patient or with a surrogate if the patient was unable to participate.

2.4. Statistics

Univariable logistic regression analysis, Chi-square, and Fisher's exact test were performed to determine potential predictors for use in a multivariable logistic regression analysis model. Factors predictive ($p < 0.15$) in univariable analysis were entered into a multivariable logistic regression analysis with backward elimination. Statistical significance was set at P-values ≤ 0.05.

3. Results

One hundred and sixty-six patients were screened at the two participating institutions, and 149 aSAH patients were enrolled from September 2012 to February 2015. Eight were deemed ineligible, 1 declined participation, 7 were excluded for poor DNA sample quality, and 1 withdrew.

3.1. Patient characteristics

Mean age of aSAH patients was 54.9 ± 12.5 years and 76.5% were female. Most ruptured aneurysms were less than 7 mm in maximum diameter (62.4%) and located in the anterior circulation (80.5%). Hunt & Hess 1–3 and modified Fisher CT 1–2 comprised 77.2% and 48.8% of the study population, respectively. Favorable functional outcome (mRS 0–2) at last follow up was achieved in 61.7% of patients (Table 1).

3.2. PHASES scores

PHASES scores ranged from 0 to 16 with a median of 5. Less than or equal to 5 was considered a low PHASES score and correlates with a 5-year risk of aneurysm rupture of 1.3%. The majority of patients had a score of 4 (20.1%) or 5 (32.2%) (Table 2 and 3).

Univariable analysis identified the following admission risk factors as predictive of poor functional outcome (mRS 3–6) at last follow up ($p < 0.15$): PHASES score, Glasgow Coma Score (GCS), modified Fisher grade, Hunt and Hess grade, history of alcohol use, and Hijdra scale score.

Following backwards elimination of GCS and Hijdra scale score, a multivariable model consisting of PHASES score, modified Fisher grade, Hunt and Hess Grade, and alcohol use identified higher PHASES scores (OR 1.235, CI 1.016–1.501, $p = 0.034$) and higher Hunt and Hess grades (OR 2.224, CI 1.353–3.655, $p = 0.002$) as independent predictors of poor functional outcome (mRS 3–6) at last follow up (Table 4; Figs. 1–3).

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