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Development Of A Clinical Decision Rule For Subarachnoid Hemorrhage Headache In The Emergency Department

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Abstract

DEVELOPMENT OF A CLINICAL DECISION RULE FOR SUBARACHNOID HEMORRHAGE HEADACHE IN THE EMERGENCY DEPARTMENT.

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Subarachnoid hemorrhage (SAH) is a neurological emergency associated with high morbidity and mortality. It has a pre-hospital mortality rate of up to 50%, and can cause severe disability or death in 40-60% of patients. A prompt diagnosis is crucial for timely work-up and intervention. It is still frequently missed, especially in alert patients who present with an acute headache as the only chief complaint. Acute headache is the 5th leading reason for Emergency Department (ED) visits. It accounts for about 3% of all ED visits in the US. Of these, ~2% will be secondary to aneurysmal SAH.

Some guidelines have emerged in recent years to help distinguish headache due to SAH from more benign causes. However, their generalizability is limited due to inclusion and exclusion criteria of individual studies, as well as unclear definitions of terminology used in criteria. This study aims to address these shortcomings by creating a generalizable clinical decision tool using a broader patient population, and providing clear definitions in a standardized questionnaire.

In this prospective observational study, 158 patients were interviewed using a standardized 15-item questionnaire. Patients eligible were alert, able to communicate and answer the questionnaires in English, and had a headache presentation unrelated to trauma. Data was used to identify differential features of headache secondary to SAH, and these features were used to create a 5-item clinical decision tool.

A total of 583 patients were eligible. Of those, 158 (27%) were enrolled, provided consent, and completed our questionnaire. Of these, 20 had SAH. After adjusting for confounders, patients with SAH were more likely to be ≥ 50 years old, experienced the "worst headache of [their] life," had headache onset during exertion, had peak intensity instantaneously (<1 second), or had associated neck stiffness/pain. We proposed two clinical decision tools using these 5 features, which had a sensitivity of 100%, negative predictive value of 100%, and negative likelihood ratio of 0, comparable to existing rules.

Thus, our decision rules agree with existing ones and perform similarly, but they have clearer definition for terminology used and can be more generalizable after external validation. (Word count: 344)

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Background

Headache presentation in the Emergency Department

Acute headache is a commonly encountered chief complaint in the Emergency Department (ED) all over the world. From 2010 to 2013, headache or pain in the head was the 4th or 5th leading cause of visits to the ED (after abdominal pain, chest pain, fever, and cough). It accounted for 2.9-3.2% of all ED visits in the US from 2010 to 2013. Headache was the chief complaint in 3,847 visits in 2013 according to the National Hospital Ambulatory Medical Care Survey (NHAMCS) [1]. Across all ambulatory care settings, headache accounts for 1% of all visits [2].

In the existing literature, headaches are often classified into primary and secondary headaches. For most purposes, patients receive a diagnosis according to the headache phenomenon that they present with at the current visit, or one they have presented with in the previous year. The International Headache Society published guidelines in 2013, named the International Classification of Headache Disorders, which helps define primary versus secondary headache disorders. Table A and B list some primary and secondary causes of headache. Primary headaches include migraine, tension-type headache, cluster headache, or one of the other trigeminal autonomic cephalalgias. Secondary headaches include new headache that is caused by another condition [3, 4].

Table A - Primary Causes of Headache [3]

- Migraine
- Tension-type headache
- Trigeminal autonomic cephalalgias
- Other primary headache disorders (e.g., new daily persistent headache…)

Table B - Secondary Causes of Headache[3]

- Headache attributed to trauma or injury to the head and/or neck
- Headache attributed to cranial or cervical vascular disorder
    - Stroke/TIA
    - Non-traumatic intracranial hemorrhage
    - Non-traumatic acute subdural hemorrhage
    - Unruptured vascular malformation (saccular aneurysm, AVM, DAVF)
    - Cavernous angioma
    - Sturge-Weber syndrome
    - Giant cell arteritis
    - Cervical or vertebral artery dissection
    - Central venous thrombosis
    - Reversible cerebral vasoconstriction syndrome
    - Subarachnoid hemorrhage
    - Pituitary apoplexy
    - Intracranial artery dissection
- Headache attributed to non-vascular intracranial disorder
    - Idiopathic intracranial hypertension
    - Post-dural puncture headache
    - Non-infectious inflammatory diseases (neurosarcoidosis, aseptic meningitis)
    - Intracranial neoplasm
    - Epileptic seizure
- Headache attributed to a substance or its withdrawal
- Headache attributed to infection
    - Viral meningitis or encephalitis
    - Bacterial meningitis or encephalitis
    - Intracranial fungal or parasitic infection
    - Brain abscess
- Headache attributed to disorder of homeostasis
- Headache or facial pain attributed to disorder of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cervical structure
- Headache attributed to psychiatric disorder
- Painful cranial neuropathies and other facial pains (trigeminal neuralgia, optic neuritis, etc.)

TIA = transient ischemic attack; AVM = arteriovenous malformation; DAVF = dural arteriovenous fistula

In the emergency department setting where resources are strained, headaches are usually divided into life-threatening, deserving more attention and diagnostic work-up, versus more benign causes. Life-threatening headaches are most often from secondary causes, both acute and chronic. Some examples include (but are not limited to): non-traumatic acute subdural hemorrhage, pituitary apoplexy, colloid cyst of the third ventricle, autonomic dysreflexia, non-traumatic subarachnoid hemorrhage, and central nervous system malignancy [3].

"Red-flag" features of Life-threatening Headaches

Nowadays, practicing physicians are more familiar with "red flag" symptoms and signs during the evaluation of headache [4]. For subarachnoid hemorrhage, they include but not limited to: sudden onset thunderclap headache, "worst headache of my life," onset associated with exertion (exercise, Valsalva, sexual intercourse), nausea, vomiting, neck stiffness, seizures, positive family history for aneurysm or aneurysmal subarachnoid hemorrhage, and positive family history for polycystic kidney disease [5]. Some red flags for meningitis in the history include: headache, photophobia, neck stiffness, fever, vomiting, altered mental status, seizures, recent brain or spine surgery, rash (meningococcemia, especially if the patient resides in high-density places like college dorm or military units), immunocompromised, and intravenous drug use. The most common presenting symptoms for cavernous sinus thrombosis is only a headache. However, any of these signs and symptoms can also be observed in more benign causes of headache including migraine, tension headache, etc., which complicate the headache evaluation and decision making process [6].

In a retrospective study of causes of sudden death associated with acute headache, investigation of 55 autopsied cases revealed the most commonly associated red flag symptoms to include: age more than 50 years, loss of consciousness and collapse, and worst/thunderclap character of headache [7, 8].

Subarachnoid Hemorrhage and Headaches

Subarachnoid hemorrhage (SAH) is the extravasation of blood into the space between the arachnoid mater and the pia mater, which normally contains cerebrospinal fluid that surrounds the central nervous system. It is a neurological emergency. Nontraumatic subarachnoid hemorrhage is most often caused by rupture of an intracranial aneurysm (accounts for 80% of nontraumatic subarachnoid hemorrhage cases [9]). There is considerable variation in the incidence of SAH in the world[10], from 2 per 100,000 in China to 22.5 per 100,000 in Finland [11]. The incidence of SAH in the US has been reported to range from 9.7 to 14.5 per 100,000 population [12-14]. It was shown in previous studies that the pooled age-adjusted incidence rate of SAH in low- to middle-income countries was almost double that of high-income countries [15, 16].

Upon admission to the hospital, SAH is usually classified based on its severity using one of multiple grading systems, namely the Glasgow Coma Scale (GCS), the Hunt & Hess (H&H) score, the World Federation of Neurologic Surgeons (WFNS) Grading System (Table C), the Ogilvy-Carter grading system, and the Fisher SAH CT grading scale.

Table C - Grading Scales for Subarachnoid Hemorrhage

Grade	Hunt-Hess Scale	WFNS* Scale
1	Mild headache, normal mental status, no cranial nerve or motor findings	GCS† score 15, no motor deficits
2	Severe headache, normal mental status, may have cranial nerve deficit	GCS score 13-14, no motor deficits
3	Somnolent, confused, may have cranial nerve or mild motor deficit	GCS score 13-14, with motor deficits
4	Stupor, moderate to severe motor deficit, may have intermittent reflex posturing	GCS score 7-12, with or without motor deficits
5	Coma, reflex posturing or flaccid	GCS score 3-6, with or without motor deficits

SAH is a serious and commonly encountered problem in the ED. One to two in 100 ED patients with headache is reported to have SAH [17]. Besides being a life-threatening neurological emergency, it also has high morbidity and mortality, with a pre-hospital mortality rate of 40-60% and can cause severe disability and low quality of life [18-21]. It is unfortunately still frequently missed due to its heterogeneous and, in some cases, seemingly benign presentation [22-25]. This is especially true in alert patients who present with an acute headache as the only complaint [26, 27]. Some important risk factors for SAH include cigarette smoking, hypertension, heavy alcohol use, and personal or family history of aneurysm, connective tissue disorder, or hemorrhagic stroke [28].

Classically, SAH presents with a "thunderclap headache," conventionally defined based on both severity and rapidity of progression: a sudden severe headache that peaks to maximum intensity in seconds to minutes [29, 30]. It can also present with or without a

* WFNS = World Federation of Neurosurgical Societies.
† Glasgow Coma Scale

"sentinel" headache (a severe headache two weeks prior to presentation, sometimes with features similar to the thunderclap headache), nuchal rigidity, decreased level of consciousness, papilledema, retinal hemorrhage, cranial nerve palsy, hemiparesis or cerebellar signs.

Initial work-up for SAH includes computed tomography (CT) of the brain without IV contrast. Non-contrast CT has a sensitivity of 98% at 12 hours, 93% at 24 hours, 80% at 72 hours, and only 50% at 1 week from the initial bleeding episode [4]. If CT does not show SAH, or the result was unequivocal but clinical suspicion remains high, cerebrospinal fluid (CSF) analysis is performed to evaluate for the presence of red blood cells and xanthochromia (from the Greek *xanthos* which means yellow and *chroma* which means color, where the cerebrospinal fluid obtained from lumbar puncture appears yellowish) [28]. Xanthochromia typically does not appear until 2-4 hours after bleeding, and is detected in 70% of patients at 3 weeks, and in 40% of patients in 1 month from the ictus [4]. The combination of non-contrast CT followed by LP for the diagnosis of SAH approaches 100% sensitivity, positive likelihood ratio of 3.03, and negative likelihood ratio of 0 within 12 hours of onset, which has been deemed sufficient to rule out subarachnoid hemorrhage [24]. Subsequent imaging may include computed tomographic angiography, catheter angiography, and magnetic resonance angiography [28]. However, the rate of misdiagnosis is still high at approximately 25% of cases, ranging from 12-64% in previous reports [17, 27, 31], mostly because it is not yet clear which patients would require and benefit from this work-up based on existing clinical decision rules and guidelines.

Existing guidelines

There are some published rules and guidelines that aim to help distinguish the life-threatening conditions from benign causes, including the SNOOP mnemonic, International Headache Society's International Classification of Headache Disorders, 3rd edition-beta (ICHD-3 beta), the Ottawa subarachnoid hemorrhage rule, and the EMERALD (Emergency Medicine, Registry Analysis, Learning and Diagnosis) subarachnoid hemorrhage rule.

The SNOOP mnemonic was proposed to help physicians remember and identify most common "red flag" symptoms to distinguish all life-threatening causes from benign ones [32, 33]. It includes:

S: Systemic symptoms (fever, weight loss), Secondary risks (HIV, cancer)

N: Neurologic symptoms/signs (altered consciousness, focal deficits)

O: Onset: sudden or split-second (think subarachnoid hemorrhage)

O: Older: new or progressive over age 50 years (think temporal arteritis)

P: Prior history: first, newly progressive, or different from usual headache; Positional (think abnormal spinal fluid pressure); Papilledema (think mass lesion, increased intracranial pressure).

This mnemonic provides an organized guide to first approach headaches. However, it does not provide a decision guideline and has not been validated in clinical practice.

The ICHD-3 (beta) [3] was established in 2013 and defined headaches in non-traumatic subarachnoid hemorrhage as typically severe and sudden, peaking within seconds

(thunderclap headache), or minutes. This headache could be the sole symptom of SAH. The diagnostic criteria for non-traumatic subarachnoid hemorrhage headache include:

A. Any new headache fulfilling criterion C
B. Subarachnoid hemorrhage in the absence of head trauma has been diagnosed
C. Evidence of causation demonstrated by at least two of the following:
    a. Headache has developed in close temporal relation to other symptoms and/or clinical signs of SAH, or has led to the diagnosis of SAH
    b. Headache has significantly improved in parallel with stabilization or improvement of other symptoms or clinical or radiological signs of SAH
    c. Headache has sudden or thunderclap onset
D. Not better accounted for by another ICHD-3 diagnosis [3]

Unfortunately, the ICHD-3 beta guideline is not easily adaptable in the clinical setting since it does not clearly state the definition used for each criterion [34, 35]. As a result, there have been other studies trying to create a clinical model more appropriate for the Emergency Department setting, including the Ottawa SAH rule and the EMERALD rule.

The Ottawa SAH rule was initially proposed to include four criteria: (1) age $\geq$ 40 years; (2) presence of neck pain or stiffness; (3) witnessed loss of consciousness or confusion; and/or (4) onset during exertion. This rule was reported to have a sensitivity of 98.5% (95% CI, 94.6% - 99.6%) and a specificity of 27.6% (95% CI, 25.7% - 29.6%). This rule was later modified to include two other variables: (5) “thunderclap headache” defined as instantly peaking pain; and (6) limited neck flexion on examination (defined as inability to touch chin

to chest or raise the head 8cm off the bed if supine). This modification led to an increase of the rule's sensitivity to 100% (95% CI, 97.2% - 100.0%) with a specificity of 15.3% (95% CI, 13.8% - 16.9%) [36]. A patient with any of these six criteria should be further worked-up to rule out subarachnoid hemorrhage. It was able to identify all patients with subarachnoid hemorrhage in the emergency department who presented with a new headache in a study involving 2131 patients. With a reported negative likelihood ratio of 0.024, which translates to about a 42-time reduction (=1/0.024) in the likelihood of subarachnoid hemorrhage, it is particularly helpful to rule-out SAH [36, 37].

Some caveats in the validation of Ottawa SAH rule should be noted, especially with its generalizability given its very specific inclusion and exclusion criteria. The study was performed and validated for adult patients 16 and older, whose chief presenting concern was a nontraumatic headache that reached maximum intensity within an hour, a Glasgow Coma Scale of 15/15, had not sustained a fall or direct head trauma in the previous 7 days, and had presented within 14 days of headache onset. Patients were also excluded from the study if they had a history of 3 or more recurrent headaches of the same character and intensity as the presenting headache over a period greater than 6 months; were referred from another hospital with a confirmed subarachnoid hemorrhage; returned for reassessment of the same headache if already investigated with both CT and lumbar puncture; had new focal neurologic findings; or had a previous diagnosis of cerebral aneurysm, subarachnoid hemorrhage, brain neoplasm, or hydrocephalus [36]. As a result, it would be challenging for many patients in the Emergency Department who presented with headache to meet all of the original criteria (for instance, having GCS 15/15). This also means that the patient must have had a thorough

neurological exam done to rule out any new focal neurological deficit before qualifying for the diagnostic rule to be used. Or in cases of patients with a family history of aneurysm, or previous chronic headache, where the rule does not apply, what clinical guideline should be followed? An external validation study done for the Ottawa SAH rule found it to be applicable to only 9% of ED patients, which greatly limited its clinical impact [38].

In trying to address some of the concerns with Ottawa SAH rule, the EMERALD SAH rule was developed in Japan, which expanded on the existing categorical predictors and added some subjective data. Their proposed two-step decision-making rule involves using Ottawa SAH rule as the first screening test, and EMERALD SAH rule as the second step. Specifically, the EMERALD SAH rule uses any of the following criteria: (1) systolic blood pressure > 150 mmHg; (2) diastolic blood pressure > 90 mmHg; (3) blood sugar > 115 mg/dL; or (4) serum potassium < 3.9 mEq/L. It was reported to have 100% sensitivity (95% CI, 98.6% - 100%) and specificity of 14.5% (95% CI, 12.5% - 16.9%). This was deemed an improvement upon the Ottawa SAH rule result when applied to this population of patient with similar sensitivity of 100% but a specificity of only 8.8% (95% CI, 7.2% - 10.7%). EMERALD also has strict inclusion/exclusion criteria similar to previous studies. For example, patients must be 15 years and older, presenting with an acute headache that must be within 14 days of onset. Patients with headache related to trauma, drugs or alcohol use, recurrent headaches, were excluded. Since it also has not been externally validated, its application is also limited.

Another point to be noted is that there are elements of these clinical decision rules not clearly specified, leaving them up to the subjective interpretation of the physicians. For instant, a thunderclap headache has only been defined as peaking "instantly." This instantaneity has never been clearly defined [30, 39-43]. Is it within a second, 5 seconds, 10 seconds, a minute, or longer? Different studies have used different definitions for thunderclap headache, which means the same variability may exist in the clinical setting due to clinicians' cognitive biases or mental models. Because of this, as well as the relatively low risk but high yield of the CT imaging and lumbar puncture combination that have now become routine in the clinical setting in the US, the utility of these clinical decision rules have been brought under scrutiny in the past few years [37, 44]. However, it can be argued that if clinical decision rules can be more generalizable, they can still have high utility in resource-poor settings where CT may not be available or too expensive, and lumbar puncture may not be safely or routinely performed, such as in Vietnam.

SAH identification in Vietnam, a resource-poor setting

Emergency medicine is a young and under-developed field in Vietnam. In his 2011 address to the First Emergency Medicine (EM) Conference in Vietnam, the Deputy Minister of Health for Vietnam announced, for the first time, the Vietnamese government's recognition of EM as a specialty [45]. The first EM residency program was also established that year. Even though healthcare infrastructure and capacity – in emergency medicine as well as in other fields – have steadily increased since then, these efforts often concentrate in tertiary care centers in populated urban cities only, with very little development in rural areas [46].

This points to a migration effect for both doctors and patients that complicates the delivery of care. Many doctors are attracted by the higher wages, better working conditions, and availability of health technologies such as radiological imaging capacity (CT, Magnetic Resonance Imaging). They then seek to work in city hospitals and clinics. From the patients' perspectives, this distribution of doctors and resources means they have to leave their hometown and go to the city for any illnesses that may require proper work-up and treatment. This is a vicious cycle that increases the burden of care on the already over-taxed tertiary centers in over-populated center cities. For instance, Ho Chi Minh Cancer Hospital reported up to 300 new diagnoses per day, and an average of greater than 2 patients per bed [47], and other hospitals in the city frequently observe up to 200% bed occupancy rate [48, 49]. One tertiary care center in Can Tho is the only ED in that region equipped to deal with emergency situations, serving 17 million residents in the Mekong Delta region [50]. As a matter of fact, occupancy of 2-4 patients per bed is not an uncommon scene in Vietnamese tertiary care centers (Figure 1).

Figure 1 - Patient overload in tertiary centers of Vietnam, leading to the common scene of patients having to share hospital beds [51].

In this setting where emergency medicine capacity was only recently created with the first generation of ED physicians still in training, and existing resources at all levels already stretched thin, there is more emphasis on the development of easy clinical decision tools for triaging patients with life-threatening headaches. Tools that are cost-effective, concise, not time-consuming, standardized, with clearly defined terminology and less room for observer biases, would be invaluable in this situation.

Statement of Purpose

Hypothesis

To date, many clinical decision rules have been created for the purpose of identifying life-threatening headaches caused by nontraumatic subarachnoid hemorrhage. However, these rules often suffer from lack of generalizability due to strict study inclusion and exclusion criteria. They often also fail to clearly define certain terminology directly used in the decision rule itself. Most notable is the variability in the definition of time to peak onset for a thunderclap headache.

The primary purpose of this study is to identify factors that are associated with increased risk of subarachnoid hemorrhage in patients presenting to the Emergency Department with acute headache among the chief presenting concerns. Our study population did not exclude those with recurrent headaches, those who were referred from another hospital, those who returned from worsening of headache, or those with headache onset more than 14 days prior to presentation. We also provided clear definitions of terms, such as time to peak onset of headache to include "less than 1 second," "less than 5 seconds," etc.

We used a 15-item questionnaire (Appendix 1) to screen all adult patients presenting with an acute headache to the Yale New Haven Hospital Emergency Department and Neurological Intensive Care Unit, then identified features in the patient's history and presentation that would put them at higher risk for subarachnoid hemorrhage. This facilitated identifying a model appropriate for a broader audience in the Emergency Department. We

also had a chance to compare how our clinical model performed compared to existing clinical decision rules in the literature.

We hypothesized that, with the broader inclusion criteria and clear terminology, we would be able to identify patients with subarachnoid hemorrhage using mainly history-focused skills with our 15-item questionnaire. In addition, we expect to show that our method can be applied more broadly but is not inferior to existing clinical rules in term of its ruling out power. This can lead to earlier and/or more appropriate diagnostic steps, referral, and treatment for this life-threatening condition, especially in resource-poor settings.

Methods

Study Design

This was a prospective, observational study at Yale-New Haven Hospital (YNHH) emergency department (ED) and Neurological Intensive Care Unit (NICU). The study was conducted over a 16-month period from September 2015 to December 2016. The study was designed by Dr. Brian MacGrory (BMG), Dr. David Greer (DG), and Linh Vu (LV, medical student), with support from physicians and other staff at the YNHH ED and NICU. The study was approved by Yale University Institutional Review Board (Yale IRB) and Yale Human Research Protection Program (HRPP).

Study Setting and Population

For the purpose of this study, the YNHH New Haven campus (including its ED, NICU, and onsite neurosurgical services) was selected as our site since it accounts for the majority of ED visits at YNHH. Yale-New Haven Hospital has about 170,000 emergency and/or urgent care visits per year. Of these, the Department of Emergency Medicine (DEM) at the New Haven campus accounts for 75% [51].

Patients were eligible for the study if they fulfilled our inclusion criteria, including: adult patients ≥ 18 years old; presented primarily for management of headache of any potential cause, and/or admitted to YNHH NICU with non-traumatic subarachnoid hemorrhage being considered as a diagnosis, whether through YNHH ED or in transfer from another hospital; presenting headache was not caused by trauma; and able to understand and

converse fluently in English. Patients <18 years old, unable to give a history of the onset of their headache for any reason (including impaired consciousness, amnesia for the event or impaired cognition at baseline), unable communicate fluently in English, or patients for whom their headache/SAH was clearly precipitated by trauma were excluded from our study. Eligible subjects were identified by Linh Vu in the ED, with the help from other study investigators and NICU fellows for the patients who presented to the NICU from outside hospitals.

Study Protocol and Measures

When a patient presented to YNHH ED with "headache," "acute headache," and "migraine" as one of their chief presenting concerns at any time during their ED visit, an automated page will be generated by the EPIC medical record system to our study investigators. When a patient was admitted to YNHH NICU service with subarachnoid hemorrhage as a potential diagnosis, either from YNHH ED or from an outside hospital (OSH), the NICU fellow on-call would notify our study investigator as well. To make sure we did not miss any patients using the two approaches above, we also screened the hospital's patient rosters daily using EPIC filters for "subarachnoid hemorrhage," "SAH," "headache," and all other variations, as well as the ED and NICU patient lists for potential missed cases.

All patients identified by our investigators were approached within 72 hours of initial presentation to the emergency department or their admission to the hospital in the case of transfer from an OSH by one of three study investigators: BMG, DG, or LV. The majority of patients were identified, interviewed, and followed-up by LV (151 out of 158 patients

enrolled, approximately 96%). All patients were asked to give informed consent. For patients who gave consent to be included in our study, a standardized 15-item questionnaire was administered. For those who did not provide informed consent, we documented basic demographic details in an anonymized fashion to account for any systematic differences in those who consented and those who did not. No identifying information was collected on those who elected not to participate in our study.

Data was collected during the period of 7AM to 5PM during weekdays. If subjects presented outside of this time window, on the weekend, or were discharged from the hospital before study investigators were able to approach them, they were contacted by telephone. In these cases, informed consent was obtained, and the questionnaire was administered via telephone.

We started the 15-item questionnaire with an open-ended question to invite patients' non-biased description with: "Please tell me about your headache." Then we asked a series of questions to gather information about the following characteristics of the patient's presenting headache:

1. Location of onset
    - Temples/temporal
    - Back of head/occipital
    - Side of head/parietal
    - Front of head/frontal
    - Around head/holocranial

- Eye
- Ear
- Neck
- Jaw
- Other (specify)

2. Side of headache
    - Right-sided
    - Left-sided
    - Both sides
    - Varied
3. Size of headache
    - Less than 6cm
    - More than 6cm
4. Time of onset
    - Started how many seconds, minutes, hours, days, weeks, or months ago
5. Duration of the headache
    - “How long did it last?” in minutes, hours, days, or ongoing headache)
6. Time to peak intensity
    - Instantaneous (less than 1 second)
    - Less than 5 seconds
    - 5 to 10 seconds
    - 10 seconds to 1 minute

- 1 to 2 minutes
- 2 to 10 minutes
- 10 to 30 minutes
- More than 30 minutes

7. Characteristic quality of the headache
    - Throbbing/pulsing
    - Pressure
    - Achy
    - Burning
    - Tight
    - Searing
    - Dull
    - Shooting
    - Stabbing
    - Other (specify)
8. Severity using a numeric scale out of 10 ("How bad is the pain on a scale of 0 to 10: where 0 is no pain and 10 is the worst?")
    - Lowest level of pain
    - Highest level of pain
9. Severity based on level of disability
    - Normal activity
    - Slight decrease in function
    - Moderate decrease in function

- Severe decrease in function
- Confined to bed

10. Associated symptoms
    - Nausea
    - Vomiting
    - Sensitivity to light
    - Sensitivity to sounds
    - Sensitivity to odors
    - Fever
    - Increased urination
    - Sore/stiff neck
    - Ringing in the ears
    - Blurred vision
    - Anxiety
    - Irritability
    - Loss of consciousness
    - Memory problems
    - Confusion
    - Eye-tearing
    - Nasal congestion
    - Eye-redness
    - Droopy eyelid
    - Other (specify)

11. Preceding symptoms ("Did you have symptoms before your headache began?")
    - One-sided weakness
    - General weakness
    - Speech difficulty
    - Double vision
    - Lightheadedness
    - Numbness/tingling
    - Loss of vision in one eye
    - Loss of vision on one side
    - Vertigo
12. Possible provoking factors ("Did anything bring on your headache?")
    - Food/beverage
        - Fasting
        - Chocolate
        - Nitrates
        - Alcoholic beverages
    - Physical exertion
        - Coughing
        - Exercise
        - Sexual intercourse
    - Medications
        - Anti-depressants

    - Illicit drugs
    - Migraine medications
- Others (specify)

13. Activities that exacerbated headache

- Lying down
- Standing up
- Exercise
- None

14. Relieving factors

- Lying down
- Standing
- Hot compress
- Cold compress
- Dark quiet room
- Keeping active/pacing
- Others (specify)

15. Presence of prior headaches

- Quantified in how many per day/week/month/year or continuous
- Quantified in the number of days in the last month patient experienced headaches or facial pain whether it be mild, moderate or severe in intensity)

- Presence of prior sentinel headache ("Have you had severe headache in the past two weeks?" and open-ended description of sentinel headache if yes).

16. Past medical history:
    - Diabetes
    - Hypertension
    - Heart disease
    - Stroke/TIA
    - Seizures/epilepsy
    - Head injury
    - Ear, nose, and throat problems
    - Dental problems
    - Cervical neck/spine problems
    - Cancer and type of cancer
    - Kidney/renal disease
    - Brain hemorrhage
    - Others (specify)

See Appendix 1 for a sample questionnaire.

Outside of the questionnaire, we also gathered basic demographic and presentation data from patients' charts, including but not limited to: age, sex, ethnicity, past medical history, weight, height, blood pressure on presentation, prior head imaging on file including CT, MRI, angiography of the head/neck, Glasgow Coma Scale (GCS) on presentation, Hunt

& Hess (HH) score on presentation. During the follow-up/observation phase, patients' records were reviewed on the day of their discharge from the hospital, with particular attention paid to those in whom the final diagnosis was nontraumatic subarachnoid hemorrhage. For those with hemorrhage, we noted the Fisher imaging grade based on imaging at presentation, and also noted the vascular territory involved, clinical grading of subarachnoid hemorrhage, presence or absence of intraventricular clot, and whether or not the hemorrhage was aneurysmal in nature.

All study data was kept in a study database. Only the principal investigator (DG) and study investigators (BMG, LV) had access to this data for the duration of the study. All information was de-identified at the earliest reasonable time after the data was received. We replaced identifying information with a deidentified code that did not directly identify the subject. Study investigator LV kept a key that linked the patient ID to the coded information. This link was kept separate, secure, and available only to the study team. Any information that could identify study participants remained confidential and was stored in an encrypted form.

Data Analysis

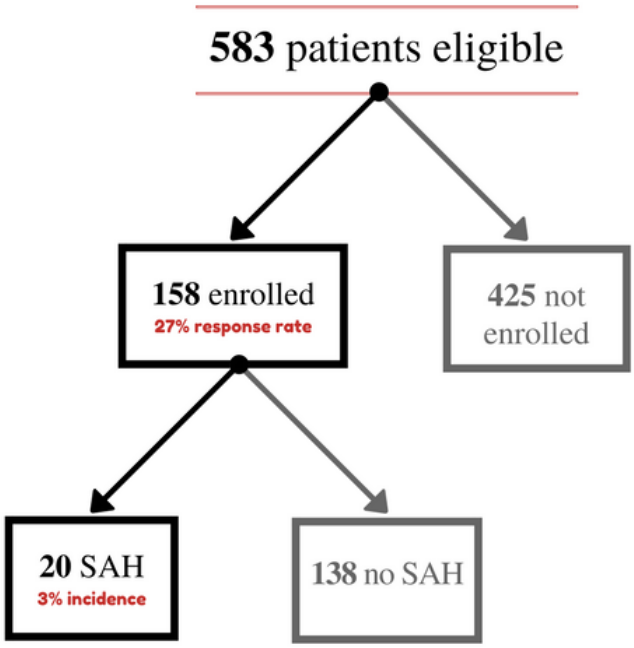
Data analysis was performed by Linh Vu. Patients who withdrew at any stage of the study were not included in the final analysis. The headaches were characterized with descriptive statistics calculated for patient demographic, clinical findings, and ED diagnoses.

Statistical analyses were performed with Fisher's exact test and Mann–Whitney's unpaired t-test. An alpha of 5% was used as a threshold for statistical significance (two-sided). We also compared proportions between groups by means of relative risks (RRs) or mean differences, as appropriate, with their corresponding 95% confidence intervals (95% CIs). Linear regression analysis was used when the outcome variable was continuous. Logistic regression analysis was used when the outcome was a binary event. Similarly, multiple logistic regression analysis was used when the outcome was a binary event. Statistical analysis was performed using STATA 14.1 (StataCorp) and SPSS 24.0 (SPSS, Inc.).

Results

Summary statistics – Enrolled vs. "Missed potentially eligible"

Figure 2 - Details of enrollment and flow of patients in study. SAH = Subarachnoid hemorrhage



There were 583 patients with headaches who presented to the YNHH ED and/or NICU over a 16-month period from September 2015 to December 2016. After applying the exclusion criteria, the study flow for these patients is shown in Figure 2. Of these, we were able to enroll 158 patients (27% enrollment rate of eligible patients), 20 of whom had a diagnosis of subarachnoid hemorrhage (3% of eligible patients). Four hundred and twenty-five patients were not enrolled into our study, from reasons including, but not limited to: patient left the Emergency Department before being approached by investigators and was not reachable by telephone; patient transferred to another hospital before being approached by investigators; patient came into the Emergency Department outside of the in-person

screening time window and was not reachable by telephone; patient did not provide full informed consent; and/or the patient did not want to be involved in study (Table D). They were considered to be "missed potentially eligible." Table E shows the basic demographic characteristics of the 158 enrolled patients versus the 425 "missed potentially eligible patients." The enrolled patients had mean age of 42 (*SD 17, range 18-85*), 74% of whom were women, 21% Hispanic, and 38% Caucasian. The "missed potentially eligible" patients had mean age of 41 (*SD 18, range 18-94*), 66% of whom were women, 25% Hispanic, and 38% Caucasian. The two groups did not differ significantly in terms of age, sex, ethnicity, or race.

Table D – Reasons for non-enrollment

- Patient left the Emergency Department before being approached by investigators and was not reachable by telephone
- Patient transferred to another hospital before being approached by investigators
- Patient came into the Emergency Department outside of the in-person screening time window and was not reachable by telephone
- Patient did not provide full informed consent

Table E - Demographic characteristics of patients identified with a headache who were enrolled versus those who were not

	Enrolled (n=158)	**Not enrolled** (n=425)	p-value
Age - *Mean (SD, range)*	42 *(17, 18-85)*	41 *(18, 18-94)*	0.41
Female sex	74%	66%	0.06
Hispanic	21%	25%	0.28
Caucasian	38%	38%	1.00

Summary statistics – Basic Demographics

Table F – Summarized demographic, presentation, and headache characteristics of enrolled participants (n=158)

Characteristics	Patients	
Age - *Mean (SD) (range)*	43 (17)	(18-85)
Age > 40 years old	84	53%
Female sex	117	74%
Hispanic	33	21%
Caucasian	60	38%
Admitted	35	22%
Onset during exertion	22	14%
Headache awoke patient from sleep	12	8%
"Worst headache of my life"	21	13%

Table F presents an overview of the social, demographic, health and headache characteristics of 158 study participants, including 20 patients (12.7%) with SAHs. Overall, participants were approximately 55 years old at intake (SD = 15, range 18-84). About half of the study participants were over 40 years old. The majority were female (74%). More than half of participants identified as Caucasian (38%), and 21% as Hispanics. Headache onset during exertion was experienced by 22 (14%) patients. Eleven (8%) reported they were awoken by a headache. Twenty-one (13%) patients reported the presenting headache to be the "worst headache of my life." Since we did not exclude patients based on headache onset, our study sees a wide spread of time since onset of headache: only 4 patients (3%) present to the ED within 1 hour of headache onset; 31 patients (20%) presented within 1 day; 23 patients (15%) presented within 1 week; and the majority (98 patients, 63%) presented more than a week after the headache first started. See Table J in Appendix 2 for details on all headache characteristics.

Regression Analysis

Table G shows the univariate correlation of selective headache characteristics, stratified by a final diagnosis of SAH versus no SAH in the first 3 columns. Overall, patients with SAH (n = 20) were significantly older than those without SAH (n = 138), with mean age of 55 versus 41, respectively ($p < 0.001$). The SAH patient population was much more likely to be over the age of 40 (85% versus 49%, $p = 0.003$), more likely to be Caucasian (65% versus 34%, $p = 0.012$), more likely to have headache onset during exertion (70% versus 6%, $p < 0.001$), headache described as "worst headache of my life," (85% versus 3%, $p < 0.001$), more likely to be occipital (55% versus 22%, $p = 0.005$) or holocranial (50% versus 25%, $p = 0.03$), more likely to have stabbing quality (35% versus 5%, $p < 0.001$), less fluctuation in severity throughout the course of the headache ($p = 0.009$), more likely to peak instantaneously in less than 1 second (65% versus 10%, $p < 0.001$) as well as in less than a minute (80% versus 17%, $p < 0.001$), associated with neck pain or stiffness (80% versus 42%, $p = 0.002$), less likely to have had prior headaches (50% versus 83%, $p = 0.002$), and less days of headache in the last month ($p < 0.001$).

Table G – Demographic and headache characteristics' association with a diagnosis of SAH using regression analysis

	SAH	**No SAH**	**Univariate** p-value	**Correlation efficient (r)**	**Multivariate** (OR, 95% CI)
No.	20 (13%)	138 (87%)			
Age - *Mean (SD)*	55 (15)	41 (16)	<0.001***	0.27***	1.1 (1.00-1.16)
Age > 40 years	85%	49%	0.003**	0.25**	11.5 (0.6-216.8)
Age > 50 years	70%	26%	<0.001***	0.31***	27.0 (1.2-635.3)*
Female sex	60%	76%	0.17		
Hispanic	10%	22%	0.25		
Caucasian	65%	34%	0.012*	0.24**	1.4 (0.1-13.5)
Admitted	100%	11%	<0.001***	-	-
Onset during exertion	70%	6%	<0.001***	0.62***	56.1 (3.7-847.6)**
Headache woke patient from sleep	15%	7%	0.29	-	
"Worst headache of my life"	85%	3%	<0.001***	0.80***	76.5 (6.0-982.5)***
Blood pressure on presentation					
SBP - *Mean (SD)*	139 (20)	135 (22)	0.38		
DBP - *Mean (SD)*	79 (15)	81 (15)	0.57		
Time since onset *(hours) - Mean (SD)*	66 (38)	828 (7538)	0.24		
Location of headache					
Temporal	10%	15%	0.74		
Occipital	55%	22%	0.005**	0.24**	-
Frontal	35%	28%	0.60		
Holocranial	50%	25%	0.03*	0.18*	-
Other	10%	9%	1.00		
Headache quality					
Throbbing/Pulsing	60%	45%	0.24		
Pressure	30%	49%	0.15		

Table G – Demographic and headache characteristics' association with a diagnosis of SAH using regression analysis

	SAH	**No SAH**	**Univariate** p-value	**Correlation efficient (r)**	**Multivariate** (OR, 95% CI)
Burning	20%	10%	0.25		
Shooting	15%	7%	0.18		
Stabbing	35%	5%	<0.001***	0.35***	-
Severity of headache *(0-10)*					
Range (max - min)	1 (2)	3 (3)	0.009**	-	-
Duration *(hours) – Mean (SD)*	135 (232)	230 (600)	0.26		
Presence of prior headaches	50%	83%	0.002**	-0.27**	-
# of days of headache in past 1 month	2 (2)	10 (11)	<0.001***	-0.24***	-
"Sentinel headache" in last 2 weeks	17%	17%	1.00		
Thunderclap headache (peak < 1 minute)	80%	17%	<0.001***	0.49***	-
Time to peak intensity					
Instantaneously (<1 second)	65%	10%	<0.001***	0.48***	11.7 (1.01-142.9)*
Less than 5 seconds	10%	2%	0.08		
Associated symptoms					
Nausea	75%	54%	0.09		
Vomiting	40%	21%	0.09		
Photophobia	60%	59%	1.00		
Phonophobia	40%	35%	0.63		
Fever	5%	12%	0.70		
Meningismus	80%	42%	0.002**	0.25**	24.4 (1.01-591.6)*
LOC or confusion	20%	22%	1.00		

LOC = Loss of consciousness

Based on the correlation efficient listed in Table G, a multivariate logistic regression model was created to adjust for potential confounders. The resultant odd ratios (ORs) for variables included in this model is reported in the last column of Table G. Most notably, the variables having a statistically significant effect that was robust to adjustments included more likely to be older than 50 years (OR 20.5, p = 0.03), headache onset during exertion (OR 56.1, p = 0.004), being described as the "worst headache of my life," (OR 76.5, p = 0.001), neck pain or stiffness (OR 24.4, p = 0.05), and time to peak intensity of less than 1 second (OR 11.7, p = 0.05). On the other hand, some variables such as occipital and holocranial location of headache, stabbing quality, presence of prior headaches, number of days of headache in the last month, presence of thunderclap headache (defined as peaking in less an a minute), being admitted to the hospital were not included in this model due to too small number of observations in each category, or because they perfectly predict SAH (e.g., all patients with SAH was admitted for treatment, so the admission variable perfectly predicted who had SAH and cannot be included in the regression model.). From this result, we created two clinical decision rules for SAH prediction, Rule 1 with 5 components as listed in Table H (age more than 50 years old, onset during exertion, "worst headache of my life," peak in less than 1 second, associated with neck pain or stiffness), and Rule 2 with 4 components without the "worst headache of my life" component.

Lastly, we applied our rules and compared the result to Ottawa SAH rule. Table H lists the screening result using each rule. Because we did not perform a physical exam in our study and did not have the criteria "limited neck flexion on physical exam" as one of the extended Ottawa SAH rule criteria, we only included the original Ottawa and (Ottawa +

presence of a thunderclap headache, defined here as peaking within 1 minute). All four rules reach a sensitivity of 100%. The specificities of Rule 1, Rule 2, Ottawa, and Ottawa + TCH are 0.7%, 37.0%, 23.9%, and 20.3%, respectively. All four rules have a negative predictive value of 100% and a negative likelihood ratio of 0.

Table H - Clinical Rules Derived from Our Study

Rule 1	**Rule 2**
• Age ≥ 50 • Onset during exertion • Peak in <1 second • Neck pain/stiffness • "Worst headache of my life"	• Age ≥ 50 • Onset during exertion • Peak in <1 second • Neck pain/stiffness

Table I - Comparison of our clinical decision rule with Ottawa SAH rule

Result assessment	**Rule 1**	**Rule 2**	**Ottawa**	**Ottawa (+TCH)**
Positive, No.				
SAH	20	20	20	20
No SAH	137	87	105	110
Negative, No.				
SAH	0	0	0	0
No SAH	1	51	33	28
Sensitivity	100.0%	100.0%	100.0%	100.0%
Specificity	0.7%	37.0%	23.9%	20.3%
Negative Predictive Value	100.0%	100.0%	100%	100%
Likelihood ratio (95% CI)				
Positive	1.01	1.59	1.31	1.25
Negative	0.00	0.00	0.00	0.00

Discussion

Our findings suggest that adult patients presenting to the emergency department with any of the following characteristics and should be considered to be at higher-risk for SAH: older than 50 years old, headache onset during exertion, the worst headache ever experienced, and associated with neck pain or stiffness. Of note, even though we reported statistically significant odd ratios for these variables and controlled for confounding factors, the confidence intervals remain large, most likely secondary to our small sample size.

Similar to age trends seen in the published literature, SAH is more often seen in adults more than 50 years old [36]. Existing clinical decision rules, including the Ottawa SAH Rule and the EMERALD SAH rule, both use 40 years old as the cut-off. However, the result from our study was only robust with a cut off of 50 years old. This can also be better applied in the resource-poor setting. In developing countries, especially those who have gone through large wars like Vietnam, the majority of the population is younger. Thus, having an older cut off age, when appropriate, would help decrease the burden on the already over-taxed healthcare system. As a result, we used 50-years-old as one of our criteria.

Except for the addition of "worst headache of my life" to our rule, the other four criteria are similar to the Ottawa SAH rule. When we excluded this variable from our clinical decision rule (Rule 2), the sensitivity stayed the same at 100%, and the specificity improved from 0.7% to 37%. Rule 2's specificity was also higher than those from Ottawa SAH rules (23.9% and 20.3%). Further validation study is needed to tease out if the rule's sensitivity and specificity truly hold up. We also found that the onset of headache in SAH was

instantaneous – defined clearly as time to peak onset of less than 1 second – instead of the other variety of "thunderclap headache" definitions. The trend observed here suggests that SAH headache has very rapid onset compared to other more benign causes of headache, such as cluster headaches which generally peak in 15 minutes or less, migraines which peak in 20 minutes to 2 hours, and tension-type headaches which peak in 4 to 6 hours [52].

Loss of consciousness or confusion was not found to be statistically significant before or after adjustments. This is different from previous literature where 40.4% of patients reported LOC at the onset of SAH, and was thought to be an important manifestation of early brain injury [7, 53-55]. It was also a component of the existing Ottawa and EMERALD SAH rules [36, 38]. The difference observed in our data and analysis may be due to the broadening of the patient population, or may be because of differences in the definition of loss of consciousness. In our study, we defined it as "passing out" per the patients, with or without a witness. Given our result, it was excluded from our rules. This exclusion of loss of consciousness and introduction of "worst headache of my life" as a variable did not significantly affect the sensitivity (100%), negative predictive value (100%), or the negative likelihood ratio (0.0) of our rules compared to the existing Ottawa SAH rule. Especially with the high sensitivity and low negative likelihood ratio, we can conclude that the likelihood of SAH is low in the absence of all 5 criteria.

With relaxing our inclusion criteria compared to existing clinical decision rules (Ottawa SAH rule, EMERALD SAH rule, etc.), we are studying a broader population, which also dilutes the prevalence and risk of SAH in our study populations. This can dilute the

target disorder in the sample, increasing generalizability but reducing precision and risking low utility if pretest probabilities are too low (making workups futile) [37]. Doing so can also make the research prohibitively expensive because we have to test a larger population to get enough SAH patients and maintain the same power for data analysis. We were aware of this trade-off when we started the project. Given our main purpose of applying these decision rules to even resource-poor settings as in the case of Vietnam to decrease triaging burden on existing resources, our focus was on increasing generalizability. We have achieved some initial results with our data, which should be expanded to a larger scale and externally validated using a different patient population.

Limitations

We acknowledge some potential limitations to this study. The exclusion criteria prevented non-English speakers from being enrolled, most of whom were Spanish speakers who were Hispanic or Latino. This prevented us from investigating SAH in Hispanic patients, who have been reported previously to have higher incidence of SAH [21]. This may have introduced a potential selection bias, which we tried to control for in our model using patient-disclosed ethnicity.

Another limitation was the small size of our SAH patient population, which restricted the power of our statistical analyses, widened our confidence intervals, increased variability in our estimated ORs, and increased the risk of overfitting in our model. Overfitting occurs when too many independent variables allow the researcher to find a relationship when in fact none exists. If overfitting occurred, it increases Type I error. As a rule of thumb, there should be at least 10 to 20 outcome events per independent variable of importance for statistical tests to be valid. Overfitting leads to large CIs for each outcome measurement, which we did notice with some variables (e.g., "Worst headache of my life" variable and headache onset during exertion variable). Since we had 158 observations, we kept the number of variables included in our model to 7 variables to prevent overfitting and decreased Type I error.

Even though our clinical decision rules have 100% sensitivity, 100% negative predictive value, and a negative likelihood ratio of 0, which makes them great for ruling out SAH, they have low specificities, which may reduce its potential impact on practice. Our tool

also has only been internally validated using our data and not been validated in other patient populations yet.

Implications and future directions

A thorough history of headache characteristics should always be obtained for all patients presenting to the emergency department with a headache. Based on our findings, patients meeting any of the following criteria should be considered at high-risk for SAH and considered for further work up with serum testing, imaging, and/or CSF analysis when appropriate:

- Patients older than 50 years
- Headache reached peak intensity instantaneously or in less than 1 second
- Headache onset during exertion (exercise, sexual intercourse)
- Worst headache ever
- Associated with neck pain or neck stiffness.

Our study was only an observational study done at a single center. A larger study should be done in the future at multiple centers to externally validate our clinical rules obtained here, as well as to increase the power and generalizability of our results.

References

1. Rui P, K.K., Albert M. *National Hospital Ambulatory Medical Care Survey: 2013 Emergency Department Summary Tables.* 2013 Jan 27, 2017]; Available from: https://www.cdc.gov/nchs/data/ahcd/nhamcs_emergency/2013_ed_web_tables.pdf.
2. Burch, R.C., et al., *The prevalence and burden of migraine and severe headache in the United States: updated statistics from government health surveillance studies.* Headache, 2015. **55**(1): p. 21-34.
3. Headache Classification Committee of the International Headache, S., *The International Classification of Headache Disorders, 3rd edition (beta version).* Cephalalgia, 2013. **33**(9): p. 629-808.
4. Rowland, L.P., T.A. Pedley, and H.H. Merritt, *Merritt's neurology*. 12th ed. 2010, Philadelphia, PA: Lippincott Williams & Wilkins. xxi, 1172 p.
5. Chu, K.H., et al., *Acute Headache Presentations to the Emergency Department: A Statewide Cross-sectional Study.* Acad Emerg Med, 2017. **24**(1): p. 53-62.
6. Edlow, J.A., et al., *Clinical policy: critical issues in the evaluation and management of adult patients presenting to the emergency department with acute headache.* Ann Emerg Med, 2008. **52**(4): p. 407-36.
7. Lynch, K.M. and F. Brett, *Headaches that kill: a retrospective study of incidence, etiology and clinical features in cases of sudden death.* Cephalalgia, 2012. **32**(13): p. 972-8.
8. Lomazow, S., *The Headache That Changed History: The Most Famous Thunderclap Headache.* Headache, 2017.
9. van Gijn, J., R.S. Kerr, and G.J. Rinkel, *Subarachnoid haemorrhage.* Lancet, 2007. **369**(9558): p. 306-18.
10. de Rooij, N.K., et al., *Incidence of subarachnoid haemorrhage: a systematic review with emphasis on region, age, gender and time trends.* J Neurol Neurosurg Psychiatry, 2007. **78**(12): p. 1365-72.
11. Ingall, T., et al., *A multinational comparison of subarachnoid hemorrhage epidemiology in the WHO MONICA stroke study.* Stroke, 2000. **31**(5): p. 1054-61.
12. Labovitz, D.L., et al., *Subarachnoid hemorrhage incidence among Whites, Blacks and Caribbean Hispanics: the Northern Manhattan Study.* Neuroepidemiology, 2006. **26**(3): p. 147-50.
13. Shea, A.M., et al., *Characteristics of nontraumatic subarachnoid hemorrhage in the United States in 2003.* Neurosurgery, 2007. **61**(6): p. 1131-7; discussion 1137-8.
14. Dority, J.S. and J.S. Oldham, *Subarachnoid Hemorrhage: An Update.* Anesthesiol Clin, 2016. **34**(3): p. 577-600.
15. Feigin, V.L., et al., *Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review.* Lancet Neurol, 2009. **8**(4): p. 355-69.
16. Connolly, E.S., Jr., et al., *Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/american Stroke Association.* Stroke, 2012. **43**(6): p. 1711-37.

17. Edlow, J.A., A.M. Malek, and C.S. Ogilvy, *Aneurysmal subarachnoid hemorrhage: update for emergency physicians.* J Emerg Med, 2008. **34**(3): p. 237-51.
18. Hop, J.W., et al., *Case-fatality rates and functional outcome after subarachnoid hemorrhage: a systematic review.* Stroke, 1997. **28**(3): p. 660-4.
19. Mayer, S. and K. Kreiter, *Quality of life after subarachnoid hemorrhage.* J Neurosurg, 2002. **97**(3): p. 741-2; author reply 742.
20. Mayer, S.A., et al., *Global and domain-specific cognitive impairment and outcome after subarachnoid hemorrhage.* Neurology, 2002. **59**(11): p. 1750-8.
21. Agostoni, E., M. Zagaria, and M. Longoni, *Headache in subarachnoid hemorrhage and headache attributed to intracranial endovascular procedures.* Neurol Sci, 2015. **36 Suppl 1**: p. 67-70.
22. Kassell, N.F., et al., *Delay in referral of patients with ruptured aneurysms to neurosurgical attention.* Stroke, 1985. **16**(4): p. 587-90.
23. Vermeulen, M.J. and M.J. Schull, *Missed diagnosis of subarachnoid hemorrhage in the emergency department.* Stroke, 2007. **38**(4): p. 1216-21.
24. Perry, J.J., et al., *Is the combination of negative computed tomography result and negative lumbar puncture result sufficient to rule out subarachnoid hemorrhage?* Ann Emerg Med, 2008. **51**(6): p. 707-13.
25. Abraham, M.K. and W.W. Chang, *Subarachnoid Hemorrhage.* Emerg Med Clin North Am, 2016. **34**(4): p. 901-916.
26. Kowalski, R.G., et al., *Initial misdiagnosis and outcome after subarachnoid hemorrhage.* JAMA, 2004. **291**(7): p. 866-9.
27. Edlow, J.A. and L.R. Caplan, *Avoiding pitfalls in the diagnosis of subarachnoid hemorrhage.* N Engl J Med, 2000. **342**(1): p. 29-36.
28. Cohen-Gadol, A.A. and B.N. Bohnstedt, *Recognition and evaluation of nontraumatic subarachnoid hemorrhage and ruptured cerebral aneurysm.* Am Fam Physician, 2013. **88**(7): p. 451-6.
29. Devenney, E., H. Neale, and R.B. Forbes, *A systematic review of causes of sudden and severe headache (Thunderclap Headache): should lists be evidence based?* J Headache Pain, 2014. **15**: p. 49.
30. Ducros, A. and M.G. Bousser, *Thunderclap headache.* BMJ, 2013. **346**: p. e8557.
31. Edlow, J.A., *Diagnosis of subarachnoid hemorrhage: are we doing better?* Stroke, 2007. **38**(4): p. 1129-31.
32. Dodick, D.W., *Diagnosing Headache: Clinical Clues and Clinical Rules.* Adv Stud Med, 2003. **3**(6C): p. 87-92.
33. Nahas, S.J., *Diagnosis of acute headache.* Curr Pain Headache Rep, 2011. **15**(2): p. 94-7.
34. Jiang, H., et al., *Field testing of the ICHD-3beta and expert opinion criteria for chronic migraine.* J Headache Pain, 2016. **17**(1): p. 85.
35. Kamm, K., et al., *[The Classification of Headache: Important Aspects of Patient's History and Clinical Diagnostic].* Dtsch Med Wochenschr, 2017. **142**(6): p. 409-417.
36. Perry, J.J., et al., *Clinical decision rules to rule out subarachnoid hemorrhage for acute headache.* JAMA, 2013. **310**(12): p. 1248-55.

37. Newman-Toker, D.E. and J.A. Edlow, *High-stakes diagnostic decision rules for serious disorders: the Ottawa subarachnoid hemorrhage rule.* JAMA, 2013. **310**(12): p. 1237-9.
38. Bellolio, M.F., et al., *External validation of the Ottawa subarachnoid hemorrhage clinical decision rule in patients with acute headache.* Am J Emerg Med, 2015. **33**(2): p. 244-9.
39. Dilli, E., *Thunderclap headache.* Curr Neurol Neurosci Rep, 2014. **14**(4): p. 437.
40. Rust, H. and H. Kimmig, *Thunderclap headache as the main symptom of an acute aortic dissection type A.* J Neurol, 2013. **260**(7): p. 1925-6.
41. Schwedt, T.J., *Thunderclap Headache.* Continuum (Minneap Minn), 2015. **21**(4 Headache): p. 1058-71.
42. Schwedt, T.J., M.S. Matharu, and D.W. Dodick, *Thunderclap headache.* Lancet Neurol, 2006. **5**(7): p. 621-31.
43. Matharu, M.S., T.J. Schwedt, and D.W. Dodick, *Thunderclap headache: an approach to a neurologic emergency.* Curr Neurol Neurosci Rep, 2007. **7**(2): p. 101-9.
44. Locker, T.E., et al., *The utility of clinical features in patients presenting with nontraumatic headache: an investigation of adult patients attending an emergency department.* Headache, 2006. **46**(6): p. 954-61.
45. Suter, R.E., *The light of emergency medicine: Vietnam-the next chapter in the global history of emergency medicine?* Acad Emerg Med, 2011. **18**(4): p. e31-5.
46. Shillabeer, A.G. and SpringerLink (Online service), *The Health of Vietnam*. p. XII, 176 p. 8 illus.
47. Shillabeer, A., *Towards an e-Health Strategy for Vietnam - Issues and Approaches.* Proceedings of the International Conference on Information Management & Evaluation, 2013: p. 44-44.
48. Shillabeer, A. and B. Anderson, *The Public Health Context in Vietnam and the Potential for Informatics.* Medinfo 2013: Proceedings of the 14th World Congress on Medical and Health Informatics, Pts 1 and 2, 2013. **192**: p. 1262-1262.
49. To K.G., G.N., Huynh V.A.N, Le A.T., *Structure of infection control and prevention in Cho Ray hospital: an analysis of the current situation.* International Journal of Infection Control, 2011. **8**(1): p. 14-20.
50. Ha, D.T., et al., *Prognostic performance of the Rapid Emergency Medicine Score (REMS) and Worthing Physiological Scoring system (WPS) in emergency department.* Int J Emerg Med, 2015. **8**: p. 18.
51. ; Available from: https://www.ynhh.org/~/media/files/annualreport/2014/ynhhstats_financials_2014.pdf).
52. Abrams, B.M., *Factors that cause concern.* Med Clin North Am, 2013. **97**(2): p. 225-42.
53. D'Souza, S., *Aneurysmal Subarachnoid Hemorrhage.* J Neurosurg Anesthesiol, 2015. **27**(3): p. 222-40.
54. Suwatcharangkoon, S., et al., *Loss of Consciousness at Onset of Subarachnoid Hemorrhage as an Important Marker of Early Brain Injury.* JAMA Neurol, 2016. **73**(1): p. 28-35.

55. Linn, F.H., et al., *Headache characteristics in subarachnoid haemorrhage and benign thunderclap headache.* J Neurol Neurosurg Psychiatry, 1998. **65**(5): p. 791-3.

Appendix 1 - 15-item questionnaire

Questionnaire

Date: _____
Name _____ Date of Birth_____ Age_____ ☐M ☐F
MRN _____

"Please tell me about your headache"

_____

_____

1. **Onset of Headache:**
   Headache started ____ seconds/minutes/hours/days/weeks/months ago (please circle the one that applies)
   days

2. **Location of Pain (check all that apply):**
   - ☐ Temples (temporal)
   - ☐ Back of head (occipital)
   - ☐ Side of head (parietal)
   - ☐ Front of head (frontal)
   - ☐ Around head (holocranial)
   - ☐ Eye
   - ☐ Ear
   - ☐ Neck
   - ☐ Jaw
   - ☐ Other_____

3. **Sidedness:**
   - ☐ Right-sided
   - ☐ Left-sided
   - ☐ Both Sides ☐ Varies

4. **Size:**
   - ☐ Less than 6cm?
   - ☐ Greater than 6cm?

5. **Pain Characteristics:**
   - ☐ Throbbing/Pulsing
   - ☐ Achy
   - ☐ Tight
   - ☐ Dull
   - ☐ Stabbing
   - ☐ Pressure
   - ☐ Burning
   - ☐ Searing
   - ☐ Shooting
   - ☐ Other_____

6. **(a) Severity** ("How bad is the pain on a scale of 0 to 10: where 0 is no pain and 10 is the worst?"):
   Lowest and highest level of pain for this headache: Low_____ to High _____

   (b) Headache disability at its worst:
   - ☐ Normal activity
   - ☐ Slight decrease in function
   - ☐ Moderate decrease in function
   - ☐ Severe decrease in function
   - ☐ Confined to bed

7. **Duration (How long did it last?):**
   Lasted ___minutes ___hours ___days
   - ☐ Headache is ongoing

8. **Prior headaches:**
   ____#/day ____#/week ____#/month ____# per year ____continuous

   (a) How many days in the last month did you experience headaches? (This includes all days of head or facial pain whether it be mild, moderate, or sever in intensity)
   _____days per month

   b) Have you had a severe headache in the past two weeks?

1

Q Yes
Q No
If YES, please tell me about it:

9. Time to peak intensity:
□ Instantly (less than 1 second)
□ Less than 5 seconds
□ 5-10 seconds
□ 10 seconds to 1 minute
□ 1-2 minutes
□ 2-10 minutes
□ **10-30 minutes**
□ **> 30 minutes**

10. Associated Symptoms:
□ Nausea
□ Vomiting
□ Sensitivity to:
□Light
□Sounds
□Odors
□ Fever
□ Increased urination
□ Sore/stiff neck
□ Ringing in the ears
□ Blurred vision
□ Anxiety
□ Irritability
□ Loss of consciousness
□ Memory problems
□ Confusion
□ Eye-tearing [Rt Lt Both] none
□ Nose congested [Rt Lt Both] none
□ Eye-redness [Rt Lt Both] none
□ Drooping eyelid [Rt Lt Both] none
□ Other:_____

11. Preceding symptoms: Did you have symptoms before your headache began?
□ One-sided weakness
□ General weakness
□ Speech difficulty
□ Double vision
□ Lightheadedness
□ Numbness/tingling none
[__Right __Left __Both]
□ Loss of vision in one eye
□ Loss of vision on one side
□Verti

12. **Provoking Factors: Did anything bring on your headache?**
Food/beverage: □ Fasting □ Chocolate □Nitrate □ Alcohol beverages
Physical exertion: □ Coughing □ Exercise □ Sexual intercourse
Medications: □ Anti-depressants □ Illicit drugs □ Migraine medications
Other Triggers:_____

13. Activity that worsens headache:
□ None
□ Lying down
□ Standing up
□ Exercise
□ Other:_____

14. Relieving Factors:
□ Lying down
□ Hot compress
□ Keeping active/Pacing
□ Standing
□ Dark quiet room
□ Cold compress
□ Other:_____

15. Have you had/do you have any of the following medical problems?
□ Diabetes
□ Hypertension
□ Heart Disease
□ Stroke/TIA
□ Seizures/epilepsy
□ Head injury
□ Ear, nose, and throat problems
□ Dental problems
□ Cervical neck/spine problems
□ Cancer
Type:_____
□ Kidney/renal disease
□ Brain hemorrhage
□ Other:_____

Appendix 2 – All headache characteristics of enrolled participants

Table J – Demographic, presentation, and headache characteristics of enrolled participants (n=158)

Characteristics	Patients	
Age - *Mean (SD) (range)*	43 (17)	(18-85)
Age > 40 years old	84	53%
Female sex	117	74%
Hispanic	33	21%
Caucasian	60	38%
Admitted	35	22%
Onset during exertion	22	14%
Headache awoke patient from sleep	12	8%
"Worst headache of my life"	21	13%
Blood pressure on presentation - *Mean (SD) (range)*		
SBP	135 (22)	(99-209)
DBP	81 (15)	(47-135)
Time since onset		
≤ 60 minutes	4	3%
~24 hours	31	20%
~7 days	23	15%
>1 week	98	63%
Location of pain (choose all that applies)		
Temporal	23	15%
Occipital	42	27%
Parietal	13	8%
Frontal	46	29%
Holocranial	45	28%
Eye	21	13%
Ear	2	1%
Neck	6	4%
Jaw	1	1%
Other	15	9%
Side of pain		
Right	22	14%
Left	27	17%

Table J – Demographic, presentation, and headache characteristics of enrolled participants (n=158)

Characteristics	Patients	
Both	102	65%
Varies	7	4%
Size of headache > 6cm	128	81%
Headache quality		
Throbbing	74	47%
Pressure	74	47%
Achy	18	11%
Burning	6	4%
Tight	5	3%
Searing	2	1%
Dull	7	4%
Shooting	12	8%
Stabbing	14	9%
Other	29	18%
Severity of headache (scale 0-10) *Mean (SD) (Range)*		
Maximum pain	8.7 (1.7)	(3-10)
Minimum pain	5.8 (3.3)	(0-10)
Change in pain intensity = (Max-Min)	2.8 (3.0)	(0-10)
Severity based on Level of Disability		
Normal activity	11	7%
Slight decrease in function	27	17%
Moderate decrease in function	40	25%
Severe decrease in function	45	28%
Confined to bed	33	21%
Duration of headache		
≤60 minutes	4	3%
~24 hours	31	20%
~7 days	23	15%
>1 week	98	63%
Presence of prior headaches	124	79%
# of days of headache in past 1 month - *Mean (SD) (range)*	9 (10.5)	(0-30)
"Sentinel headache" in last 2 weeks	9	17%
Thunderclap headache (peak < 1 minute)	39	25%

Table J – Demographic, presentation, and headache characteristics of enrolled participants (n=158)

Characteristics	Patients	
Time to peak onset		
Instantly (<1 second)	27	17%
Less than 5 seconds	4	3%
5-10 seconds	5	3%
10 seconds – 1 minute	3	2%
1-2 minutes	2	1%
2-10 minutes	19	12%
10-30 minutes	9	6%
>30 minutes	88	56%
Associated symptoms		
Nausea	89	56%
Vomiting	37	23%
Photophobia	93	59%
Phonophobia	56	35%
Osmophobia	14	9%
Fever	17	11%
Polyuria	14	9%
Meningismus	74	47%
Tinnitus	25	16%
Blurry vision	65	41%
Anxiety	43	27%
Irritability	31	20%
Loss of consciousness	13	8%
Memory problem	18	11%
Confusion	28	18%
Teary eye (right)	7	4%
Teary eye (left)	3	2%
Teary eye (both)	32	20%
Nasal congestion (right)	5	3%
Nasal congestion (left)	1	1%
Nasal congestion (both)	24	15%
Red eye (right)	1	1%
Red eye (left)	1	1%

Table J – Demographic, presentation, and headache characteristics of enrolled participants (n=158)

Characteristics		Patients
Red eye (both)	11	7%
Ptosis (right)	2	1%
Ptosis (left)	1	1%
Ptosis (both	1	1%
Other	75	48%
Preceding symptoms	14	9%
One-sided weakness	0	0%
General weakness	5	3%
Speech difficulty	0	0%
Double vision	1	1%
Lightheadedness	8	5%
Numbness/tingling	3	2%
Loss of vision in one eye	0	0%
Loss of vision on one side	0	0%
Vertigo	3	2%
Provoking factors	52	33%
Food/Drinks		
Fasting	5	3%
Chocolate	3	2%
Nitrates	0	0%
Alcohol beverages	4	3%
Physical exertion		
Coughing	5	3%
Exercise	5	3%
Sexual intercourse	1	1%
Any exertion	22	14%
Medications		
Anti-depressants	0	0%
Illicit drugs	0	0%
Migraine medications	0	0%
Other triggers	38	24%
Activity that worsens headache		
Lying down	25	16%

Table J – Demographic, presentation, and headache characteristics of enrolled participants (n=158)

Characteristics		Patients
Standing up	30	19%
Exercise	25	16%
Any activity	79	50%
Other	42	27%
Relieving factors		
Lying down	45	28%
Standing	2	1%
Hot compress	1	1%
Cold compress	18	11%
Dark quiet room	54	34%
Keeping active/Pacing	2	1%
Other	46	29%
Past medical problems		
Diabetes	14	9%
Hypertension	51	32%
Heart disease	8	5%
Stroke/TIA	4	3%
Seizures/Epilepsy	6	4%
Head injury	2	1%
Ear, nose, and throat problems	5	3%
Dental problems	1	1%
Cervical neck / spine problems	11	7%
Cancer	9	6%
Kidney/renal disease	9	6%
Brain hemorrhage	2	1%
Other	81	51%