Nontraumatic Subarachnoid Hemorrhage in the Setting of Negative Cranial Computed Tomography Results: External Validation of a Clinical and Imaging Prediction Rule

Dustin G. Mark, MD; Yun-Yi Hung, PhD; Steven R. Offerman, MD; Adina S. Rauchwerger, MA; Mary E. Reed, DrPH; Uli Chettipally, MD, MPH; David R. Vinson, MD; Dustin W. Ballard, MD, MBE; for the Kaiser Permanente CREST Network Investigators

Study objective: Clinical variables can reliably exclude a diagnosis of nontraumatic subarachnoid hemorrhage in patients with negative cranial computed tomography (CT) results. We externally validated 2 decision rules with 100% reported sensitivity for a diagnosis of subarachnoid hemorrhage, among patients undergoing lumbar puncture after a negative cranial CT result: (1) clinical rule: presence of any combination of age 40 years and older, neck pain or stiffness, loss of consciousness, or headache onset during exertion; and (2) imaging rule: cranial CT performed within 6 hours of headache onset.

Methods: This was a matched case-control study of patients presenting to 21 emergency departments between 2000 and 2011. Patients with a diagnosis of subarachnoid hemorrhage as determined by lumbar puncture after a negative cranial CT result were screened for inclusion. A matched control cohort was selected among patients with a diagnosis of headache after negative cranial CT and lumbar puncture results.

Results: Fifty-five cases of subarachnoid hemorrhage meeting inclusion criteria were identified, 34 (62%) of which were attributed to cerebral aneurysms. External validation of the clinical rule demonstrated a sensitivity of 97.1% (95% confidence interval [CI] 88.6% to 99.7%), a specificity of 22.7% (95% CI 16.6% to 29.8%), and a negative likelihood ratio of 0.13 (95% CI 0.03 to 0.61) for a diagnosis of subarachnoid hemorrhage. External validation of the imaging rule revealed that 11 of 55 subarachnoid hemorrhage cases (20%) had negative cranial CT results for tests performed within 6 hours of headache onset.

Conclusion: The clinical rule demonstrated useful Bayesian test characteristics when retrospectively validated against this patient cohort. The imaging rule, however, failed to identify 20% of subarachnoid hemorrhage patients with a negative cranial CT result. [Ann Emerg Med. 2013;62:1-10.]

Please see page 2 for the Editor's Capsule Summary of this article.

A **feedback** survey is available with each research article published on the Web at www.annemergmed.com.
A **podcast** for this article is available at www.annemergmed.com.

0196-0644/$-see front matter

http://dx.doi.org/10.1016/j.annemergmed.2012.09.003

INTRODUCTION

Background

Approximately 1% to 4% of emergency department (ED) visits for headache are attributable to nontraumatic subarachnoid hemorrhage, with an annual incidence of 1 in 10,000 among the general population.[1-5] Approximately 80% of subarachnoid hemorrhage cases are due to ruptured cerebral aneurysms, for which delays in treatment increase risks of rebleeding and resultant disability or death.[3,6-8] Timely recognition of subarachnoid hemorrhage is particularly challenging among patients with normal neurologic examination results and mental status, with estimated rates of missed diagnoses ranging between 5% and 12%.[1,2,7-18]

The standard diagnostic evaluation for subarachnoid hemorrhage uses noncontrast cranial computed tomography (CT) followed by lumbar puncture if the imaging result is normal, an approach that has 100% sensitivity and 67% specificity for the diagnosis of subarachnoid hemorrhage.[19] The majority of subarachnoid hemorrhage cases are identified by cranial CT, with reported sensitivities ranging from 93% to 100% with third- to sixth-generation CT technologies when imaging is performed within 12 to 24 hours of headache onset.[5,20-30] In one large prospective study, 1 additional

Editor's Capsule Summary

What is already known on this topic

A previously derived clinical decision rule identified variables associated with a low risk for subarachnoid hemorrhage in headache patients with a negative unenhanced brain computed tomography (CT) result.

What question this study addressed

This 55-case case-control study attempted to validate the clinical decision rule and assess the sensitivity of CT performed within 6 hours of headache onset.

What this study adds to our knowledge

The clinical decision rule identified 97.1% of the patients with subarachnoid hemorrhage. CT performed within 6 hours of headache onset was falsely negative in 11 patients.

How this is relevant to clinical practice

Further validation of the rule is needed in diverse populations. Negative CT result for tests performed within 6 hours of headache onset does not rule out subarachnoid hemorrhage.

diagnosis of subarachnoid hemorrhage was made for every 90 lumbar punctures performed after a negative cranial CT result.[20]

Considering the high sensitivity of cranial CT for detecting subarachnoid hemorrhage early in the course of headache, the benefit and utility of lumbar puncture in this setting has been questioned.[5,20,22,24,25,29,30] False-positive lumbar puncture results owing to traumatic technique result in potentially harmful diagnostic testing and may occasionally lead to surgical treatment of incidentally discovered aneurysms, which have a background prevalence of 1% to 2%.[31] Unfortunately, no particular findings can reliably distinguish cerebrospinal fluid abnormalities attributable to traumatic technique during lumbar puncture from true abnormalities caused by subarachnoid hemorrhage.[3,32-35] The limited specificity of lumbar puncture is reflected by a 2.5-fold higher rate of negative angiography study results among patients with subarachnoid hemorrhage despite negative cranial CT results compared with that of patients with subarachnoid hemorrhage evident on cranial CT.[36]

Importance

Given the morbid consequences of missed diagnoses of subarachnoid hemorrhage, more than 95% of emergency physicians would welcome a clinical decision tool to help risk-stratify patients with sudden-onset headaches.[37] The largest reported prospective study of an ED population with acute headache has suggested several combinations of high-risk clinical variables (including age ≥40 years, neck pain, loss of consciousness, and onset of headache with exertion) that, if absent, might allow clinicians to safely forgo diagnostic testing for subarachnoid hemorrhage, given 100% sensitivity (95% confidence interval [CI] 97.1% to 100%) for a diagnosis of subarachnoid hemorrhage.[38] A second analysis from the same prospective cohort also reported 100% sensitivity (95% CI 97.0% to 100%) for noncontrast cranial CT when performed within 6 hours of headache onset.[20] However, only 7% of patients with subarachnoid hemorrhage in this cohort received a diagnosis by lumbar puncture after negative cranial CT results. Thus, the validity of that study's findings for patients presenting without visible subarachnoid blood on cranial CT remains uncertain.

Goals of This Investigation

We externally validated the aforementioned clinical and imaging-based prediction rules among a population of patients receiving a diagnosis of subarachnoid hemorrhage despite negative initial cranial CT results.

MATERIALS AND METHODS

Selection of Participants

A case-control study was performed through review of charts (both written and electronic) from patients treated at Northern California Kaiser Permanente EDs between 2000 and 2011. The Kaiser Foundation Research Institute's Northern California institutional review board approved the study. Patients were screened for case inclusion if they had an ED visit with a related *International Statistical Classification of Diseases and Related Health Problems, Ninth Edition* (*ICD-9*) diagnosis code of subarachnoid hemorrhage (430), along with both a noncontrast cranial CT and cerebrospinal fluid analysis performed during the ED encounter. Local facility radiologists, who were not required to have advanced training in neuroradiology, made the final interpretation of CT images. Case inclusion criteria were age older than 18 years, CT without evidence of subarachnoid blood by final documented radiologist interpretation, normal documented neurologic examination result (aside from isolated single cranial nerve deficits), greater than 5 RBCs per microliter of cerebrospinal fluid, and at least 1 of the following criteria as evidence of subarachnoid hemorrhage: presence of xanthochromia on visual inspection of cerebrospinal fluid, angiographic evidence of cerebral aneurysm or arteriovenous malformation, or subsequent cranial imaging (such as magnetic resonance imaging [MRI]) demonstrating subarachnoid hemorrhage performed within 48 hours after the index lumbar puncture. Cases were excluded from the study if patients had a known untreated cerebral aneurysm or arteriovenous malformation, underwent lumbar puncture before CT, or had documentation of head trauma occurring within the 4 weeks before the index presentation. The use of 5 RBCs per microliter of cerebrospinal fluid as a cutoff value is based on a clinical consensus reached by Perry et al[19,20,38] in previous research.[39]

After identification of cases, to evaluate the specificity of the clinical rule among patients with a negative cranial CT result and suspected subarachnoid hemorrhage, a matched control group was selected among patients with an ED-related *ICD-9* diagnosis code of headache (784 and 339) and both noncontrast cranial CT and cerebrospinal fluid analysis performed during the ED encounter. Controls were matched to cases by year and presenting ED in a ratio of 3 controls for every case, in an attempt to control for variations in ED practice and CT technology over time. The primary inclusion criterion was a documented concern for subarachnoid hemorrhage in the emergency physician chart according to the presenting complaints. Exclusion criteria were identical to those of cases, with the addition of the following: microbiologic evidence of infection in cerebrospinal fluid samples (by culture, antigen testing, or polymerase chain reaction testing), presumed immunocompromised status (known infection with HIV, solid organ transplant recipient, active hematologic cancer, active chemotherapy, or steroid use of >10 mg prednisone equivalents per day for 4 weeks or more), more than 5 RBCs or WBCs per microliter of cerebrospinal fluid, or the presence of visible cerebrospinal fluid xanthochromia. This method of control cohort selection was believed to be adequate for the purposes of excluding false-negative subarachnoid hemorrhage diagnoses, in agreement with a recent prospective study.[19]

Methods of Measurement

Two emergency physicians conducted a structured explicit chart review and abstraction of records.[39] The abstractors were trained by the lead author (D.G.M.) after joint review of representative charts, using a standardized abstraction form. Missing data were coded as undocumented, and ambiguous or apparently conflicting data were adjudicated by majority consensus among 3 investigators. Abstractor interrater reliability was based on an 18% random sample of study patient charts and is reported as percentage agreement.

The following variables were abstracted from the ED record, including age, race, sex, triage vital signs, and pain score (1 to 10 scale), time of headache onset, time from onset to peak intensity (sudden versus gradual, sudden defined as the explicit documentation of a "sudden onset," "thunderclap," or "explosive" headache), headache duration (constant versus intermittent), headache quality (sharp versus throbbing or dull), headache location (frontal, temporal, occipital, diffuse, migratory), presence of new neck stiffness or pain, presence of new back pain, history of vomiting since headache onset, loss of consciousness at headache onset, exertion at headache onset, and complaints of light sensitivity, visual changes, or hearing changes. The electronic medical record was also examined for a history of hypertension or renal insufficiency (estimated glomerular filtration rate <60 mL/minute), social history of smoking or sympathomimetic drug use (past or present), and current use of pharmaceutical antiplatelet or anticoagulant agents. Additionally, all pertinent operative, procedure, and discharge summary reports were examined. Laboratory values on initial presentation were obtained from an independent electronic database (peripheral blood hematocrit level, cerebrospinal fluid cell counts, and microbiologic analysis), as were final transcribed interpretations of radiologic imaging studies (including CT, MRI, and catheter angiography). Clinical neurologic grade at hospital discharge (modified Rankin Scale) was determined with discharge summary reports, using a previously described systematic methodology.[40]

CT examinations were performed with either single-slice helical scanning technology or, in the majority of cases, multislice cine technology (ie, fifth- and sixth-generation CT). Written reports and physical or digital copies of radiology studies (when available) were examined to determine the computed tomogram manufacturer and model and protocol used. Protocols varied between medical centers and over time, with supratentorial imaging slice thickness ranging from 5 to 10 mm and posterior fossa slice thickness ranging from 2.5 to 7 mm.

Outcome Measures and Primary Data Analysis

An 11-year span was chosen to allow an adequate number of cases of subarachnoid hemorrhage diagnosed after an initial normal cranial CT result. We estimated the total number of nontraumatic subarachnoid hemorrhage cases diagnosed within the health plan during this period to be approximately 1,000, according to a previous study of aneurysmal subarachnoid hemorrhage within the same health plan during a 10-year period.[41] According to an average reported sensitivity of cranial CT for subarachnoid hemorrhage between 92% and 96%, we anticipated that between 40 and 80 cases would be available for inclusion.[25] Assuming a case sample size of 70, the expected 95% CI for a decision rule with 100% sensitivity would be 95% to 100%.

Undocumented data were imputed with Rubin's multiple imputation method through the PROC MI procedure in SAS, version 9.1 (SAS Institute, Inc., Cary, NC).[42] This method replaces each missing value with a set of plausible values, in this case 5 permutations for each missing value, creating multiple completed data sets. Results from the analysis of these data sets were then averaged and combined with SAS procedure PROC MIANALYZE.

External validation of decision rules previously reported to have a 100% sensitivity for the diagnosis of subarachnoid hemorrhage were undertaken with the case and control data sets.[20,38] These rules are (1) clinical rule: presence of any combination of age 40 years and older, neck pain or stiffness, loss of consciousness, or headache onset during exertion; and (2) imaging rule: cranial CT performed within 6 hours of headache onset. Rules incorporating arrival by ambulance as a predictor variable were not validated because of lack of reliable documentation.[38]

A sensitivity analysis was performed by using bootstrap analysis, with 1,000 iterations to assess the stability of the clinical rule against the data set. The bootstrap samples were generated with SAS procedure PROC SURVEYSELECT.[43]

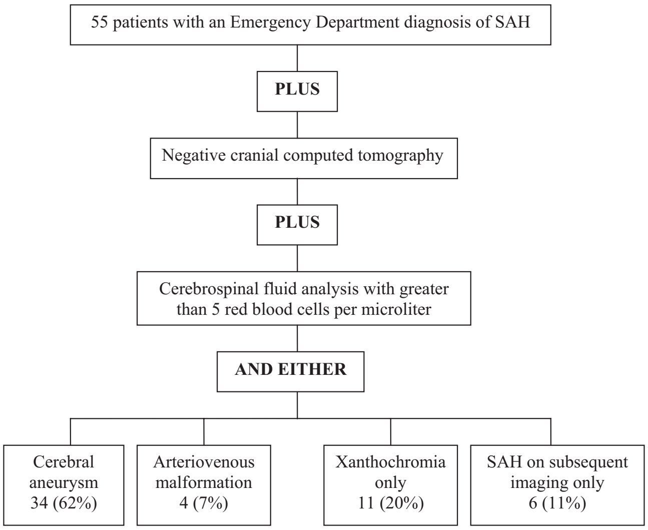

Figure. Case inclusion criteria. SAH, Subarachnoid hemorrhage.

The 2.5th and 97.5th percentiles of the 1,000 bootstrap samples are considered an approximation of the 95% CI.[44]

All univariate, bivariate, and multivariate analyses were performed with SAS, version 9.13. Categorical variables were analyzed with χ^2 or Fisher's exact tests. Continuous variables were analyzed with Student's *t* test or the Wilcoxon rank-sum test as appropriate.

RESULTS

Characteristics of Study Subjects

Fifty-six patients meeting our case definition were identified, of whom 55 had full records available for chart abstraction and are included in the data set (Figure). One-hundred sixty-eight controls were selected with the methodology outlined above. Demographics and clinical characteristics (excluding those variables with >40% missing data) for both cases and controls are listed in Table 1.

After the diagnosis of subarachnoid hemorrhage in the ED, 52 of 55 patients (95%) underwent further investigation for vascular causes with catheter-directed 4-vessel cerebral angiography. Two additional patients underwent magnetic resonance angiography alone, and a single patient with xanthochromia on cerebrospinal fluid analysis was later found to have a hemorrhagic schwannoma in the thoracic spine.

Thirty-eight of the 55 cases (69%) were found to have either a cerebral aneurysm or arteriovenous malformation on vascular imaging. Thirty-seven of these 38 patients underwent subsequent endovascular or operative intervention. One patient with xanthochromic cerebrospinal fluid was found to have several 1- to 2-mm aneurysms on formal angiography, which were considered incidental and managed conservatively. Only 22 of these patients (58%) with proven vascular causes demonstrated visual evidence of xanthochromia on cerebrospinal fluid analysis.

Table 1. Patient characteristics.

Variable	Case (n=55)	Control (n=168)
Age, mean (SD, range), y	52 (15, 22–92)	48 (17, 18–87)
Female, No. (%)	34 (62)	125 (74)
History of hypertension, No. (%)	22 (40)	49 (29)
History of migraine headaches, No. (%)	7 (13)	26 (15)
Ethnicity, No. (%)		
White	29 (53)	74 (44)
Asian	13 (24)	23 (14)
Black	5 (9)	18 (11)
Hispanic	7 (13)	35 (21)
Other/unknown	1 (2)	18 (11)
Triage vital signs, mean (SD)		
Initial systolic blood pressure (mmHg)	158 (25)	149 (26)
Initial diastolic blood pressure (mmHg)	87 (15)	84 (15)
Initial pulse rate	76 (15)	81 (15)
Pain score (range 1–10)	8.2 (1.8)	7.8 (2.4)
Rate of headache onset, No. (%)		
Sudden	41 (75)	108 (64)
Gradual	8 (15)	29 (17)
Undocumented	6 (11)	31 (18)
Worst headache of life, No. (%)		
Yes	36 (65)	72 (43)
No	3 (5)	8 (5)
Undocumented	16 (29)	88 (52)
Headache onset to CT time, No. (%), h		
Up to 6	11 (20)	63 (38)
Up to 12	17 (31)	79 (47)
Up to 24	19 (35)	105 (63)
Up to 48	27 (49)	124 (74)
>48	28 (51)	40 (24)
Undocumented	0	4 (2)
Headache duration, No. (%)		
Constant	49 (89)	136 (82)
Intermittent	3 (6)	29 (18)
Undocumented	3 (5)	3 (2)
Headache location, No. (%)*		
Occipital	19 (35)	45 (27)
Temporal	4 (7)	53 (32)
Frontal	12 (22)	48 (29)
Other (diffuse, top, migratory)	9 (15)	25 (15)
Undocumented	18 (33)	34 (20)
Neck pain or stiffness, No. (%)		
Yes	39 (71)	46 (27)
No	10 (18)	112 (67)
Undocumented	6 (11)	10 (6)
Loss of consciousness, No. (%)		
Yes	7 (13)	8 (5)
No	48 (87)	159 (95)
Undocumented	0	1 (1)
Vomiting, No. (%)		
Yes	28 (51)	53 (32)
No	27 (49)	114 (68)
Undocumented	0	1 (1)

Table 1. Continued.

Variable	Case (n=55)	Control (n=168)
Onset during activity, No. (%)		
Yes	13 (24)	8 (5)
No	24 (44)	96 (57)
Undocumented	18 (33)	64 (38)
Photophobia, No. (%)		
Yes	16 (29)	43 (26)
No	21 (38)	102 (61)
Undocumented	18 (33)	23 (14)
Vision changes, No. (%)		
Yes	5 (9)	18 (11)
No	31 (56)	131 (78)
Undocumented	19 (35)	19 (11)
Smoking history, No. (%)		
Yes	12 (22)	41 (24)
No	36 (65)	113 (67)
Undocumented	7 (13)	14 (8)
Sympathomimetic drug use, No. (%)		
Yes	1 (2)	6 (4)
No	41 (75)	149 (89)
Undocumented	13 (24)	13 (8)
Antiplatelet or anticoagulant drug use, No. (%)		
Yes	10 (18)	24 (14)
No	41 (75)	139 (83)
Undocumented	4 (7)	5 (3)
Hematocrit level <30%, No. (%)	1 (2)	3 (2)
Calculated glomerular filtration rate <60 mL/min, No. (%)	4 (7)	6 (4)

*Some patients have more than 1 headache location.

Of patients without evidence of a vascular cause of subarachnoid hemorrhage identified on initial imaging, 25% underwent a second cerebral angiographic study between 10 and 21 days later, without any further identification of vascular causes. All patients were discharged from index hospitalization with excellent functional neurologic status (modified Rankin Scale=0 or 1). Fifty-four of 55 patients were alive at 6 months, with 1 patient dying from pneumonia deemed unrelated to index hospitalization and treatment of subarachnoid hemorrhage.

Main Results

External validation of the clinical rule after multiple imputation of undocumented variables revealed a sensitivity of 97.1% (95% CI 88.6% to 99.7%), a specificity of 22.7% (95% CI 16.6% to 29.8%), and a negative likelihood ratio of 0.13 (95% CI 0.03 to 0.61) for a diagnosis of subarachnoid hemorrhage (Table 2). These point estimates for sensitivity and specificity are the average estimates after multiple imputation of undocumented variables. Sensitivity analysis of an additional 1,000 bootstrapped iterations demonstrated stability of these point estimates (Table E1, available online at http://www.annemergmed.com).

External validation of the imaging rule revealed less than 100% sensitivity; 11 patients with subarachnoid hemorrhage had a negative cranial CT result within 6 hours of headache onset. Seven of the 11 patients had a cerebral vascular cause of subarachnoid hemorrhage identified (aneurysm or arteriovenous malformation). Details of the imaging characteristics for each of the 11 cases with cranial CT performed within 6 hours of headache onset are found in Table 3.

The overall percentage agreement for the externally validated variables was 96.6% between the 2 study chart abstractors (Table 4). Individual percentage agreement values were as follows: age (100%), neck pain or stiffness (90.2%), loss of consciousness (100%), headache onset with exertion (97.6%), and time from headache onset to CT of less than 6 hours (95.1%).

LIMITATIONS

Although to our knowledge this data set represents the largest single published cohort of subarachnoid hemorrhage cases with negative CT and positive lumbar puncture results, the retrospective case identification methodology used could introduce a diagnostic bias by effectively excluding possible "missed" subarachnoid hemorrhage patients who did not undergo lumbar puncture after cranial CT, as well as patients who did not receive a diagnosis of subarachnoid hemorrhage by the emergency physician. We chose emergency physician diagnoses of subarachnoid hemorrhage over hospital discharge diagnoses, given that in the latter case a formal diagnosis of subarachnoid hemorrhage could be discounted after normal vascular imaging results (approximately 20% of nontraumatic subarachnoid hemorrhage cases lack attributable angiographic abnormalities).[3] It is likely, however, that less clinically evident cases are underrepresented in this case series.

There is also the possibility that some of the cerebral aneurysms reported in this study were detected incidentally in the setting of either a false-positive cerebrospinal fluid result or a nonaneurysmal cause of subarachnoid hemorrhage. We were unable to establish definitive confirmation of aneurysm rupture as the cause of subarachnoid hemorrhage, such as gross pathologic finding of clotted blood surrounding an aneurysm. The absence of cerebrospinal fluid xanthochromia among 42% of patients with presumed vascular subarachnoid hemorrhage causes may seem to support this assumption; however, this rate is consistent with that of multiple previous studies demonstrating low sensitivity of cerebrospinal fluid visual inspection for xanthochromia.[32-34,45]

The retrospective nature of data collection through clinical chart review presents a potential source of reporting bias, as represented by missing variables requiring imputation. It is probable that among missing variables, pertinent negative results were more likely to be undocumented as opposed to pertinent positive results, and thus imputation may overestimate sensitivity and underestimate specificity. However, imputation was performed mostly for the benefit of an estimated specificity

Table 2. External validation of a clinical decision rule to identify patients with subarachnoid hemorrhage.*

Clinical Decision Rule	Percentage (95% CI) Sensitivity	Percentage (95% CI) Specificity	Negative Likelihood Ratio
Presence of any of the following Age ≥40 y Neck pain or stiffness Loss of consciousness Headache onset during exertion	97.1 (88.6–99.7)	22.7 (16.6–29.8)	0.13 (0.03–0.61)

*After multiple imputation of missing variables, the previously derived clinical decision rule was retrospectively applied to a cohort of 55 patients with proven nontraumatic subarachnoid hemorrhage in the setting of a negative cranial CT result, along with 168 control patients with negative cranial CT and lumbar puncture results. The decision rule states that patients warrant investigation for subarachnoid hemorrhage if any of the following variables are present: (1) age 40 years and older, (2) neck pain or stiffness, (3) loss of consciousness, and (4) onset of headache during exertion. Sensitivity and specificity are presented in terms of the ability of the rule to predict a diagnosis of subarachnoid hemorrhage among patients with a negative cranial CT result and clinical suspicion of subarachnoid hemorrhage.

Table 3. Characteristics of patients with subarachnoid hemorrhage and negative results for CT performed within 6 hours of headache onset.

Age/Sex	Year	CT Scanner	CT Slice Thickness, mm/mm*	Cerebrospinal Fluid RBCs/Microliter†	Xanthochromia	Angiography Results
65/F	2004	GE Lightspeed 16 (16 slice)	5/5	7,282	No	7-mm PCOM aneurysm
67/F	2010	GE Lightspeed VCT (64 slice)	5/5	408,000	No	6-mm PCOM aneurysm
34/F	2002	Phillips Tomoscan-SR 7000 (single-slice helical)	5/5	690,000	No	Arteriovenous malformation
63/F	2003	Unavailable	5/5	43,720	No	PCOM aneurysm (unknown size)
76/F	2010	GE Lightspeed VCT (64 slice)	5/5	517,500	No	4-mm PCOM aneurysm
50/F	2006	Unavailable	7.5/7	22,500	No	7-mm basilar tip aneurysm
92/F	2007	Unavailable	5/5	280,000	Yes	5-mm ACOM aneurysm
30/F	2001	GE HiSpeed CT/I (single-slice helical)	7/7	93	Yes	Negative catheter angiography result
38/F	2002	Unavailable	5/5	673	Yes	Negative catheter angiography result
67/M	2010	GE Lightspeed VCT (64 slice)	5/5	320,000	No	Negative catheter angiography result
56/M	2009	GE Lightspeed VCT (64 slice)	5/5	119,000	No	Negative catheter angiography result

F, Female; *PCOM*, posterior communicating artery; *ACOM*, anterior communicating artery; *M*, male.
*Minimum slice thickness through supratentorial planes/posterior fossa.
†In final collection tube.

Table 4. Interrater reliability for abstracted variables used in the external validation.*

Variable	Percentage Agreement
Age	100.0
Neck pain or stiffness	90.2
Loss of consciousness	100.0
Headache onset with exertion	97.6
Performance of cranial CT within 6 h of headache onset	95.1
Overall percentage agreement	96.6

*Percentage agreement between the 2 study chart abstractors was based on an 18% random sample of study patient charts.

among the control data set. The clinical rule still demonstrated excellent sensitivity of 94.5% for a diagnosis of subarachnoid hemorrhage when we excluded the variable with the highest reported rate of missing data (onset of headache with exertion) and analyzed the data set without any imputation (data not shown).

Finally, our study did not reach our goal enrollment of 70 case patients and thus had wider CIs for our point estimates of test characteristics than desired. Despite these limitations, considering the paucity of existing data concerning this particular subset of patients, we believe this investigation provides externally valid guidance to clinicians in their shared decisionmaking with patients undergoing evaluation for subarachnoid hemorrhage after a negative cranial CT result.

DISCUSSION

The goal of this research project is to help clinicians further refine their testing strategies for subarachnoid hemorrhage, specifically among patients with suspected subarachnoid hemorrhage despite negative cranial CT results, through external validation of preexisting decision rules. We report here that the clinical decision rule validates well, though not perfectly, when applied to this patient subset. The utility of the clinical rule is amplified by the fact that the imaging rule failed to identify 20% of the patients in this series who had a cranial CT performed within 6 hours of headache onset, demonstrating that even prompt cranial CT cannot be used as a stand-alone test to definitively rule out subarachnoid hemorrhage.

Although the decision rules derived by Perry et al[38] performed well at reducing the likelihood of subarachnoid hemorrhage before any diagnostic testing, there were a number of serious alternative diagnoses detected by cranial CT among the derivation population (such as intracerebral hemorrhage and brain tumor, representing 0.9% of the population). The clinical decision rule was neither designed nor tested for its ability to safely identify these patients. However, only a single alternative diagnosis (bacterial meningitis) was detected by cerebrospinal fluid sampling in that study, with an incidence of 0.05% among the studied population.

Ultimately, the cornerstone to any applied testing strategy, along with informed patient consent to further testing, is a reasonable estimate of pretest disease probability. Unfortunately, most data sets estimating the prevalence of subarachnoid hemorrhage among ED patients with acute headache are highly subject to enrollment bias. Two prospective studies of patients presenting to either an ED or a cohort of general practitioners with the "worst headache of my life" or sudden and severe headaches reported subarachnoid hemorrhage rates of 17% and 25%, respectively, with an incidence of 12% to 14% among patients with normal neurologic examination results.[5,46] More recently, Perry et al[38] enrolled 1,999 patients in a prospective ED study of sudden-onset headache or syncope associated with a headache in the absence of focal neurologic deficits. In contrast to previous prospective studies, the incidence of subarachnoid hemorrhage in this study was 6.5%. When 1,050 additional patients not enrolled but deemed likely eligible for the study were included, the overall rate of subarachnoid hemorrhage was 5.2%. A second report from this prospective data set revealed a 7.7% incidence of subarachnoid hemorrhage among 3,132 patients undergoing noncontrast cranial CT.[20] These data sets are arguably more representative of the incidence of subarachnoid hemorrhage among the general ED population with acute headache than those of previous prospective studies.

Several studies have been published about the sensitivity of noncontrast cranial CT for detecting subarachnoid hemorrhage, with estimates ranging from 93% to 100%.[5,20,23-25,29,30] If we assume an overall sensitivity of 93% and 99.9% specificity, we can estimate that the negative likelihood ratio of a negative cranial CT result for nontraumatic subarachnoid hemorrhage is 0.07. Using a 7% prevalence of disease among alert patients with acute headache, this leaves us with a posterior probability of subarachnoid hemorrhage around 1 in 200.

However, given the time-varying sensitivity of cranial CT for subarachnoid hemorrhage, it is more appropriate to subdivide patients according to time from ictus when evaluating testing strategies.[26,29,47] According to Perry et al,[20] patients who were imaged within 6 hours of ictus had an observed subarachnoid hemorrhage incidence of 12.7%. The reported sensitivity of cranial CT performed within 6 hours of ictus in that study was 100% (95% CI 97.0% to 100%), yielding posterior probability estimates between zero and 1 in 230. Conversely, 17 of 119 patients with subarachnoid hemorrhage were not identified by cranial CT when imaged more than 6 hours from headache onset, resulting in a sensitivity of 85.7% (95% CI 78.3% to 90.9%). Even with a lower observed disease prevalence of 5.5% among this subset, the corresponding number needed to test with lumbar puncture is estimated to be between 80 and 204. Although this represents a relatively low posterior probability of disease, many physicians still pursue testing for subarachnoid hemorrhage even when estimating a pretest probability of less than 2%.[48] Likewise, a survey of emergency physicians about their willingness to use clinical decision rules for subarachnoid hemorrhage indicated a median required sensitivity of 99% for such a rule, with 1 of 5 clinicians suggesting that 100% sensitivity would be required.[37]

Although cranial CT or clinical prediction rules alone do not clearly and safely achieve these ideal test performance goals, the combined application of both testing strategies might offer an improvement. Even with a very conservative estimated subarachnoid hemorrhage risk of 1.25% (1 of 80 risk) after negative cranial CT, the application of the 4-item decision rule derived by Perry et al,[38] even with a negative likelihood ratio as high as 0.13 as reported in this study, can reduce this incidence to 0.2%, or 1 in 500 patients. Additionally, given that the specificity for the rule in this study was validated against a population of patients who uniformly underwent cerebrospinal fluid analysis, application of the clinical rule after negative cranial CT result has the potential to reduce rates of lumbar puncture by approximately 25%.

Reported absolute increases in morbidity rates resulting from missed diagnoses of subarachnoid hemorrhage range between 5% and 25%.[10,11,13-16,49-51] Kowalski et al[11] reported an unadjusted odds of 3.4 (95% CI 1.3 to 8.9) for death or severe disability at 3 months among patients who presented with Hunt-Hess grade I or II at misdiagnosis. Although recall bias has been raised as a potential flaw in these studies, this concern has been somewhat mitigated by a systematic review that reported a lower incidence of retrospectively reported sentinel headaches among control patients with nonaneurysmal subarachnoid hemorrhage or with stroke (around 5%) as opposed to patients with aneurysmal subarachnoid hemorrhage (10% to 43%).[52] Additionally, an older randomized trial of aneurysmal subarachnoid hemorrhage treatment strategies, which included a conservative management pathway of bed rest, reported a mortality rate of 48% among patients treated conservatively who were found to have no or minor symptoms (headache, meningeal irritation, diplopia) at randomization.[6]

Authors point to these studies when citing the need for testing with lumbar puncture to prevent the morbidity and mortality associated with the delayed diagnosis and treatment of subarachnoid hemorrhage.[3,53,54] However, only 7% of patients with missed diagnosis of subarachnoid hemorrhage in the study by Kowalski et al[11] failed to undergo lumbar puncture after negative cranial CT results, whereas 73% did not have either CT or lumbar puncture performed. Additionally, though limited by the use of administrative data and lack of adjustment for clinical status at presentation, a review of 1,507 ED patients receiving a diagnosis of subarachnoid hemorrhage found a lower unadjusted crude 30-day mortality rate among patients with a probable undiagnosed subarachnoid hemorrhage–related presentation in the 2 weeks before index subarachnoid hemorrhage diagnosis (6.2% versus 33.9%).[13]

Although none of these studies truly address the outcome of the untreated patient with evidence of subarachnoid hemorrhage by lumbar puncture despite normal cranial CT result, treated patients appear to fare very well. The cooperative aneurysm study found that 92.7% of patients with aneurysmal subarachnoid hemorrhage who presented alert and without evidence of blood on CT had good or excellent recovery at 6 months.[55] Ultimately, the physician and patient must engage in a shared decisionmaking process about the perceived and desired risks and benefits surrounding any medical test or treatment.[56] Research conducted among ED patients with possible acute coronary syndrome suggests that patients often have much higher risk thresholds for themselves than do the treating physicians.[57] Along these lines, it is our hope that the application of the clinical decision rule will help clinicians feel more confident when informing patients of their absolute risk of subarachnoid hemorrhage after a negative cranial CT result, allowing them to make well-informed recommendations and fully engage in the shared decisionmaking process.

In conclusion, the previously derived clinical decision rule for subarachnoid hemorrhage demonstrated useful discriminatory characteristics when externally validated among a subset of patients with subarachnoid hemorrhage in the setting of negative cranial CT result. Performance of cranial CT within 6 hours of headache onset, however, failed to identify 20% of the cases in this study. These findings provide further guidance to clinicians interested in applying the clinical decision rule during shared decisionmaking with patients who have a negative cranial CT result. Such a testing strategy might achieve a mutually acceptable low pretest probability of disease and reduce rates of invasive testing accordingly. Clinicians should note that these findings are derived from a limited patient cohort within a single integrated health system and thus may not adequately represent other practice settings.

Supervising editor: John Sarko, MD

Author affiliations: From the Department of Emergency Medicine, Kaiser Permanente, Oakland, CA (Mark); the Division of Research, Kaiser Permanente Northern California, Oakland, CA (Hung, Rauchwerger, Reed); the Department of Emergency Medicine, Kaiser Permanente, South Sacramento, CA (Offerman); the Department of Emergency Medicine, Kaiser Permanente, South San Francisco, CA (Chettipally); the Department of Emergency Medicine, Kaiser Permanente, Roseville, CA (Vinson); and the Department of Emergency Medicine, Kaiser Permanente, San Rafael, CA (Ballard).

Author contributions: DGM, SRO, ASR, MER, UC, DRV, and DWB conceived the study and obtained research funding. DGM and Y-YH refined participant and variable selection. DGM and SRO undertook chart abstraction and managed the data, including quality control. Y-YH and MER provided statistical advice on study design and analyzed the data. DGM drafted the article, and all authors contributed substantially to its revision. DGM takes responsibility for the paper as a whole.

Funding and support: By *Annals* policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article as per ICMJE conflict of interest guidelines (see www.icmje.org). The authors have stated that no such relationships exist. Funded by a Kaiser Permanente Northern California Community Benefits grant.

Publication dates: Received for publication June 29, 2012. Revisions received August 11, 2012, and August 25, 2012. Accepted for publication September 7, 2012. Available online September 29, 2012.

Presented at the Society for Academic Emergency Medicine meeting, May 2012, Chicago, IL.

Address for correspondence: Dustin G. Mark, MD, E-mail dustin.g.mark@kp.org.

REFERENCES

1. Ramirez-Lassepas M, Espinosa CE, Cicero JJ, et al. Predictors of intracranial pathologic findings in patients who seek emergency care because of headache. *Arch Neurol*. 1997;54:1506-1509.
2. Perry JJ, Stiell I, Wells G, et al. Diagnostic test utilization in the emergency department for alert headache patients with possible subarachnoid hemorrhage. *CJEM*. 2002;4:333-337.
3. Edlow JA, Caplan LR. Avoiding pitfalls in the diagnosis of subarachnoid hemorrhage. *N Engl J Med*. 2000;342:29-36.
4. Leicht MJ. Non-traumatic headache in the emergency department. *Ann Emerg Med*. 1980;9:404-409.
5. Morgenstern LB, Luna-Gonzales H, Huber JC Jr, et al. Worst headache and subarachnoid hemorrhage: prospective, modern computed tomography and spinal fluid analysis. *Ann Emerg Med*. 1998;32(3 pt 1):297-304.
6. Nishioka H, Torner JC, Graf CJ, et al. Cooperative study of intracranial aneurysms and subarachnoid hemorrhage: a long-term prognostic study. II. Ruptured intracranial aneurysms managed conservatively. *Arch Neurol*. 1984;41:1142-1146.
7. Nibbelink DW, Torner JC, Henderson WG. Intracranial aneurysms and subarachnoid hemorrhage—report on a randomized treatment study. IV-A. Regulated bed rest. *Stroke*. 1977;8:202-218.
8. Kassell NF, Boarini DJ, Adams HP Jr, et al. Overall management of ruptured aneurysm: comparison of early and late operation. *Neurosurgery*. 1981;9:120-128.
9. Nibbelink DW, Knowler LA. Cooperative study of intracranial aneurysms and subarachnoid hemorrhage. Report on a randomized treatment study. II. Objectives and design of randomized aneurysm study. *Stroke*. 1974;5:552-556.
10. Mayer PL, Awad IA, Todor R, et al. Misdiagnosis of symptomatic cerebral aneurysm. Prevalence and correlation with outcome at four institutions. *Stroke*. 1996;27:1558-1563.
11. Kowalski RG, Claassen J, Kreiter KT, et al. Initial misdiagnosis and outcome after subarachnoid hemorrhage. *JAMA*. 2004;291:866-869.
12. Molyneux AJ, Kerr RS, Birks J, et al. Risk of recurrent subarachnoid haemorrhage, death, or dependence and standardised mortality ratios after clipping or coiling of an intracranial aneurysm in the International Subarachnoid Aneurysm Trial (ISAT): long-term follow-up. *Lancet Neurol*. 2009;8:427-433.

13. Vermeulen MJ, Schull MJ. Missed diagnosis of subarachnoid hemorrhage in the emergency department. *Stroke*. 2007;38: 1216-1221.
14. Vannemreddy P, Nanda A, Kelley R, et al. Delayed diagnosis of intracranial aneurysms: confounding factors in clinical presentation and the influence of misdiagnosis on outcome. *South Med J*. 2001;94:1108-1111.
15. Ritz R, Reif J. Comparison of prognosis and complications after warning leaks in subarachnoidal hemorrhage—experience with 214 patients following aneurysm clipping. *Neurol Res*. 2005;27: 620-624.
16. Jakobsson KE, Saveland H, Hillman J, et al. Warning leak and management outcome in aneurysmal subarachnoid hemorrhage. *J Neurosurg*. 1996;85:995-999.
17. Neil-Dwyer G, Lang D, Smith P, et al. Outcome after aneurysmal subarachnoid haemorrhage: the use of a graphical model in the assessment of risk factors. *Acta Neurochir (Wien)*. 1998;140: 1019-1027.
18. Kassell NF, Torner JC, Jane JA, et al. The International Cooperative Study on the Timing of Aneurysm Surgery. Part 2: surgical results. *J Neurosurg*. 1990;73:37-47.
19. Perry JJ, Spacek A, Forbes M, 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;51:707-713.
20. Perry JJ, Stiell IG, Sivilotti ML, et al. Sensitivity of computed tomography performed within six hours of onset of headache for diagnosis of subarachnoid haemorrhage: prospective cohort study. *BMJ*. 2011;343:d4277. doi: 10.1136/bmj.d4277.
21. Cortnum S, Sorensen P, Jorgensen J. Determining the sensitivity of computed tomography scanning in early detection of subarachnoid hemorrhage. *Neurosurgery*. 2010;66:900-902; discussion 903.
22. Carstairs SD, Tanen DA, Duncan TD, et al. Computed tomographic angiography for the evaluation of aneurysmal subarachnoid hemorrhage. *Acad Emerg Med*. 2006;13:486-492.
23. Byyny RL, Mower WR, Shum N, et al. Sensitivity of noncontrast cranial computed tomography for the emergency department diagnosis of subarachnoid hemorrhage. *Ann Emerg Med*. 2008; 51:697-703.
24. Lourenco AP, Mayo-Smith WW, Tubbs RJ, et al. Does 16-detector computed tomography improve detection of non-traumatic subarachnoid hemorrhage in the emergency department? *J Emerg Med*. 2009;36:171-175.
25. Gee C, Dawson M, Bledsoe J, et al. Sensitivity of newer-generation computed tomography scanners for subarachnoid hemorrhage: a Bayesian analysis. *J Emerg Med*. 2012;43:13-18.
26. Edlow JA, Wyer PC. Evidence-based emergency medicine/clinical question. How good is a negative cranial computed tomographic scan result in excluding subarachnoid hemorrhage? *Ann Emerg Med*. 2000;36:507-516.
27. Sidman R, Connolly E, Lemke T. Subarachnoid hemorrhage diagnosis: lumbar puncture is still needed when the computed tomography scan is normal. *Acad Emerg Med*. 1996;3:827-831.
28. Sames TA, Storrow AB, Finkelstein JA, et al. Sensitivity of new-generation computed tomography in subarachnoid hemorrhage. *Acad Emerg Med*. 1996;3:16-20.
29. van der Wee N, Rinkel GJ, Hasan D, et al. Detection of subarachnoid haemorrhage on early CT: is lumbar puncture still needed after a negative scan? *J Neurol Neurosurg Psychiatry*. 1995;58:357-359.
30. Boesiger BM, Shiber JR. Subarachnoid hemorrhage diagnosis by computed tomography and lumbar puncture: are fifth generation CT scanners better at identifying subarachnoid hemorrhage? *J Emerg Med*. 2005;29:23-27.
31. Schievink WI. Intracranial aneurysms. *N Engl J Med*. 1997;336: 28-40.
32. Perry JJ, Sivilotti ML, Stiell IG, et al. Should spectrophotometry be used to identify xanthochromia in the cerebrospinal fluid of alert patients suspected of having subarachnoid hemorrhage? *Stroke*. 2006;37:2467-2472.
33. MacDonald A, Mendelow AD. Xanthochromia revisited: a re-evaluation of lumbar puncture and CT scanning in the diagnosis of subarachnoid haemorrhage. *J Neurol Neurosurg Psychiatry*. 1988;51:342-344.
34. Arora S, Swadron SP, Dissanayake V. Evaluating the sensitivity of visual xanthochromia in patients with subarachnoid hemorrhage. *J Emerg Med*. 2010;39:13-16.
35. Heasley DC, Mohamed MA, Yousem DM. Clearing of red blood cells in lumbar puncture does not rule out ruptured aneurysm in patients with suspected subarachnoid hemorrhage but negative head CT findings. *AJNR Am J Neuroradiol*. 2005;26:820-824.
36. Vermeulen M, van Gijn J. The diagnosis of subarachnoid haemorrhage. *J Neurol Neurosurg Psychiatry*. 1990;53:365-372.
37. Perry JJ, Eagles D, Clement CM, et al. An international study of emergency physicians' practice for acute headache management and the need for a clinical decision rule. *CJEM*. 2009;11:516-522.
38. Perry JJ, Stiell IG, Sivilotti ML, et al. High risk clinical characteristics for subarachnoid haemorrhage in patients with acute headache: prospective cohort study. *BMJ*. 2010;341: c5204.
39. Allison JJ, Wall TC, Spettell CM, et al. The art and science of chart review. *Jt Comm J Qual Improv*. 2000;26:115-136.
40. Raina KD, Callaway C, Rittenberger JC, et al. Neurological and functional status following cardiac arrest: method and tool utility. *Resuscitation*. 2008;79:249-256.
41. Zaroff JG, Leong J, Kim H, et al. Cardiovascular predictors of long-term outcomes after non-traumatic subarachnoid hemorrhage. *Neurocrit Care*. 2011. doi: 10.1007/s12028-011-9592-x.
42. Barnard J, Meng XL. Applications of multiple imputation in medical studies: from AIDS to NHANES. *Stat Methods Med Res*. 1999;8:17-36.
43. Cassell DL. Don't be loopy: re-sampling and simulation the SAS way. SAS Global Forum. Orlando, FL; April 16-19, 2007. Paper 183-2007.
44. Miller DP. Bootstrap 101: obtain robust confidence intervals for any statistic. SUGI 29. Montreal, Canada; May 9-12, 2004. Paper 193-29.
45. Wood MJ, Dimeski G, Nowitzke AM. CSF spectrophotometry in the diagnosis and exclusion of spontaneous subarachnoid haemorrhage. *J Clin Neurosci*. 2005;12:142-146.
46. Linn FH, Wijdicks EF, van der Graaf Y, et al. Prospective study of sentinel headache in aneurysmal subarachnoid haemorrhage. *Lancet*. 1994;344:590-593.
47. Adams HP Jr, Kassell NF, Torner JC, et al. CT and clinical correlations in recent aneurysmal subarachnoid hemorrhage: a preliminary report of the Cooperative Aneurysm Study. *Neurology*. 1983;33:981-988.
48. Perry JJ, Stiell IG, Wells GA, et al. Attitudes and judgment of emergency physicians in the management of patients with acute headache. *Acad Emerg Med*. 2005;12:33-37.
49. Dorsch NW. Cerebral aneurysms and the "missed" hemorrhage. *Aust N Z J Med*. 1986;16:486-490.
50. Leblanc R. The minor leak preceding subarachnoid hemorrhage. *J Neurosurg*. 1987;66:35-39.
51. Verweij RD, Wijdicks EF, van Gijn J. Warning headache in aneurysmal subarachnoid hemorrhage. A case-control study. *Arch Neurol*. 1988;45:1019-1020.

52. Polmear A. Sentinel headaches in aneurysmal subarachnoid haemorrhage: what is the true incidence? a systematic review. *Cephalalgia*. 2003;23:935-941.
53. Adams HP Jr, Jergenson DD, Kassell NF, et al. Pitfalls in the recognition of subarachnoid hemorrhage. *JAMA*. 1980;244:794-796.
54. van Gijn J. Slip-ups in diagnosis of subarachnoid haemorrhage. *Lancet*. 1997;349:1492.
55. Adams HP Jr, Kassell NF, Torner JC. Usefulness of computed tomography in predicting outcome after aneurysmal subarachnoid hemorrhage: a preliminary report of the Cooperative Aneurysm Study. *Neurology*. 1985;35:1263-1267.
56. Moreau A, Carol L, Dedianne MC, et al. What perceptions do patients have of decision making (DM)? toward an integrative patient-centered care model. A qualitative study using focus-group interviews. *Patient Educ Couns*. 2012;87:206-211.
57. Hess EP, Knoedler MA, Shah ND, et al. The chest pain choice decision aid: a randomized trial. *Circ Cardiovasc Qual Outcomes*. 2012;5:251-259.

Table E1. Sensitivity analysis of the clinical decision rule: a sensitivity analysis performed using 1000 bootstrapped samples.

Clinical Decision Rule	Sensitivity (95% CI)	Specificity (95% CI)
Presence of *any* of the following: • Age 40 years and older • Neck pain or stiffness • Loss of consciousness • Headache onset during exertion	97.1 (96.2–98.0)	22.7 (21.4–24.2)