Sensitivity of Early Brain Computed Tomography to Exclude Aneurysmal Subarachnoid Hemorrhage

A Systematic Review and Meta-Analysis

Nicole M. Dubosh, MD; M. Fernanda Bellolio, MD; Alejandro A. Rabinstein, MD; Jonathan A. Edlow, MD

Background and Purpose—Emerging evidence demonstrating the high sensitivity of early brain computed tomography (CT) brings into question the necessity of always performing lumbar puncture after a negative CT in the diagnosis of spontaneous subarachnoid hemorrhage (SAH). Our objective was to determine the sensitivity of brain CT using modern scanners (16-slice technology or greater) when performed within 6 hours of headache onset to exclude SAH in neurologically intact patients.

Methods—After conducting a comprehensive literature search using Ovid MEDLINE, Ovid EMBASE, Web of Science, and Scopus, we conducted a meta-analysis. We included original research studies of adults presenting with a history concerning for spontaneous SAH and who had noncontrast brain CT scan using a modern generation multidetector CT scanner within 6 hours of symptom onset. Our study adheres to the preferred reporting items for systematic reviews and meta-analyses (PRISMA).

Results—A total of 882 titles were reviewed and 5 articles met inclusion criteria, including an estimated 8907 patients. Thirteen had a missed SAH (incidence 1.46 per 1000) on brain CTs within 6 hours. Overall sensitivity of the CT was 0.987 (95% confidence intervals, 0.971–0.994) and specificity was 0.999 (95% confidence intervals, 0.993–1.0). The pooled likelihood ratio of a negative CT was 0.010 (95% confidence intervals, 0.003–0.034).

Conclusions—In patients presenting with thunderclap headache and normal neurological examination, normal brain CT within 6 hours of headache is extremely sensitive in ruling out aneurysmal SAH. **(*Stroke*. 2016;47:750-755. DOI: 10.1161/STROKEAHA.115.011386.)**

Key Words: brain ■ cerebrospinal fluid ■ confidence intervals ■ headache ■ subarachnoid hemorrhage

Headache accounts for ≈2% of all emergency department (ED) visits.[1] A subset of these patients present with abrupt onset of a severe headache reaching peak intensity within 60 s referred to as a thunderclap headache.[2] The most serious cause of thunderclap headache is aneurysmal subarachnoid hemorrhage (SAH), which accounts for 4% to 12% of ED patients with a thunderclap headache.[3–6] Current clinical practice calls for a noncontrast computed tomography (CT) of the brain followed by a lumbar puncture (LP) if the CT scan is negative to exclude SAH.[7–10] This is because the sensitivity of CT scans for detecting subarachnoid blood ranges from 90% to 100% when performed within the first 24 hours after symptom onset. The sensitivity decreases as time from onset to CT elapses because the blood is progressively diluted by the normal flow of cerebrospinal fluid.[6,11–16]

Recent data suggest that in neurologically intact patients, the sensitivity of modern CT scanners for SAH approaches 100% when performed within 6 hours of headache onset and interpreted by qualified radiologists.[11,13,17–20] These data suggest that in this early-presenting population, an LP is not necessary to rule out SAH and an initial negative CT can be considered a rule-out test. An LP is associated with patient anxiety and discomfort and can be complicated by postprocedure headache (15%–20% of patients).[21] Traumatic taps, which occur in 10% to 15% of patients, may lead to unnecessary vascular imaging and other downstream consequences.[3,20–22]

We conducted a systematic review and meta-analysis to determine the diagnostic accuracy of early CT only in the diagnosis of spontaneous SAH. Our objective was to determine the sensitivity, specificity, and positive and negative

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From the Department of Emergency Medicine, Beth Israel Deaconess Medical Center, Boston, MA (N.M.D., J.A.E.); Department of Emergency Medicine, Harvard Medical School, Boston, MA (N.M.D., J.A.E.); Departments of Emergency Medicine (M.F.B.) and Neurology (A.A.R.), Mayo Clinic, Rochester, MN.

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Correspondence to Nicole M. Dubosh, MD, Department of Emergency Medicine, Beth Israel Deaconess Medical Center, One Deaconess Rd, W-CC2, Boston, MA 02215. E-mail ndubosh@bidmc.harvard.edu

likelihood ratios (LRs) of a brain CT performed within 6 hours of headache onset using modern generation scanners in the diagnosis of spontaneous SAH.

Methods

Study Design

This was a systematic review and meta-analysis, and it adheres to the preferred reporting items for systematic reviews and meta-analyses (PRISMA).[23]

Eligibility Criteria

We included original research studies of adults with a history concerning for spontaneous nontraumatic SAH and evaluated with noncontrast brain CT scan using modern generation multidetector scanners (16-slice CT technology or greater) within 6 hours of headache onset. Studies involving traumatic SAH, patients younger than 15 years of age, nonhuman studies, older generation scanners, and those in which CT was not performed within 6 hours of headache onset were excluded.

Search Strategy

An expert librarian designed a comprehensive search strategy with input from the authors. The electronic search included Ovid MEDLINE, Ovid EMBASE, Web of Science, and Scopus from inception (Ovid MEDLINE and Scopus 1966, Ovid EMBASE 1988 and Web of Science 1975) until April 2015. See Appendix I in the online-only Data Supplement for the terms used in the search. We adjusted the search strategy to account for differences in indexing between databases. Web of Science and Scopus depend heavily on text words, so acronyms were included. We did not apply a language restriction. We also reviewed the related citations: section of PubMed, reference lists of included studies, and the authors' personal collections.

Study Selection

Two investigators (N.M.D. and A.A.R.) independently screened the titles and abstracts of all records identified from the search strategy (phase I). If either reviewer thought the study might be eligible, we obtained the full report. The same 2 investigators then independently assessed the eligibility of each full report (phase II). We used Cohen unweighted κ to measure chance corrected agreement between reviewers. Discrepancies were resolved by a third author (J.A.E.).

Quality Assessment and Risk of Bias

Data on study quality and risk of bias were abstracted for each study by 1 author (M.F.B.). We assessed the quality of studies of diagnostic accuracy with the revised Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool.[24]

Data Extraction

Two authors (N.M.D. and A.A.R.) independently extracted data from each included article using a standardized data extraction form. We extracted the following data from each study: design, patient demographics, definition of SAH, CT technology, type of radiologist interpreting the CT, clinical setting, number of patients with SAH, and number of missed cases of SAH. When possible, we collected data to construct a 2 by 2 table, including true negatives, true positives, false negatives, and false positives. When data were not sufficiently reported, we sought other sources of information, such as letters to the editors, authors' reports, and personal e-mail to the authors to acquire missing information.

Data Synthesis

Diagnostic accuracy measures were pooled using random-effect meta-analysis[25] as implemented in OpenMeta[Analyst][26] and tested in a bivariate mixed effects regression model.[27] We used a random effects model because it calculates more conservative 95% confidence intervals (CI) and the effects of treatment are assumed to vary around the overall average treatment effect. This is recommended when data are heterogeneous. Results are presented as incidence per 1000 patients and we calculated pooled sensitivity, specificity, LR of a positive and a negative test with 95% CI. LR is the likelihood that a given test result would be expected in a patient with the target disorder (SAH) compared with the likelihood that that same result would be expected in a patient without the target disorder (SAH). It is a different way to incorporate sensitivity and specificity and provide a direct estimate of how much a test result will change the odds of having the disease. LR equals sensitivity/(1 specificity), and the LR of a negative test indicates how much the odds of the disease (SAH) decrease when the CT is negative.

The sensitivity, specificity, and LRs are properties of the test. The positive and negative predictive values are properties of both the test and the population being tested. The predictive value of a test in 2 populations with different disease prevalence will be different.

When a cell has zero count in the 2 by 2 tables, the statistical software will correct adding +0.5 count to all the cells. Meta-analysis heterogeneity was assessed using the I^2 statistic.[28]

Sensitivity Analysis

We performed an a priori selected sensitivity analysis to exclude the studies with data obtained through letters to the editor and communication with the authors.

Results

Description of Included Studies

Figure 1 shows the study selection process. The search strategy yielded 882 articles. After screening titles and abstracts and removing duplicates, we identified 40 potentially relevant studies. Two authors (N.M.D. and A.A.R.) abstracted data independently and in duplicate. Interobserver agreement for phase II of the review was 87.5% (κ, 0.64; 95% CI, 0.36–0.91) indicating good agreement between reviewers. After full-text review, 5 articles were included in the meta-analysis. The reasons for exclusion after full-text review were that the article did not specify data for patients imaged within 6 hours, the article was not an original study, and the article did not pertain to SAH.

Study Characteristics

The characteristics of the included studies are shown in Table. Four were cohort studies that reported diagnostic test accuracy, and one was a case-control study. Four had retrospective design[13,18,20,29] and one was prospective.[11] We estimated that

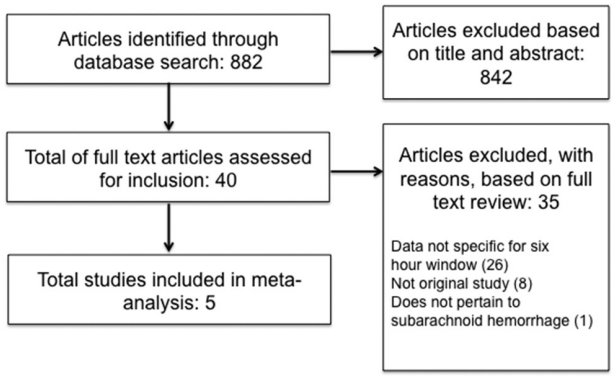

Figure 1. Flow diagram of study selection.

Table. Characteristics and Results of Studies Included in Meta-Analysis

Study*	Type/Setting	Patient Population	% With SAH Within 6 h	% Who Underwent LP	Who Read Final CT	6-hour Miss Rate	6-hour Sensitivity
Perry et al,[11] n=3136	Prospective cohort	Neurologically intact ED patients with HA concerning for SAH	12.7% (121/953)	49.4% (1546/3122)	Neuroradiologist or general radiologist	0% (0/240)	100%
Backes et al,[13] n=250	Retrospective cohort	ED patients suspicious for SAH, normal LOC, no focal deficits	50.4% (69/137)	100% (69/69)	Neuroradiologist	1.5% (1/69)	98.6%
Stewart et al,[18] n=244	Retrospective cohort	ED patients screened for SAH	47.7% (31/65)	100% (179/179)	Radiology consultant	0% (0/31)	100%
Mark et al,[29] n = 55	Retrospective, case control	Only analyzed CT negative patients, Included 21 EDs >11 y	20% (11/55 cases) in the study. Incidence of SAH on the population not reported	100% (55/55)	General radiologist	20% among CT negative patients (11 of 55 cases had missed SAH among 1000 true positives in the same time period)	Sensitivity of CT reported as <100%
Blok et al,[20] n=760	Retrospective	ED patients with spontaneous acute HA concerning for SAH, neurologically intact	One missed case (1/52) was a nonaneurysmal perimesenphalic hemorrhage. Incidence of SAH on the population not reported	100% (760/760)	Neuroradiologist and experienced stroke neurologist	0.1% (1/760)	100%

CT indicates computed tomography; ED, emergency department; HA, headache; LOC, level of consciousness; LP, lumbar puncture; and SAH, subarachnoid hemorrhage.

*Note the incidence of SAH is on cases reported in the study and not in the population where the study was conducted.

a total of 8907 patients underwent CT within 6 hours. See Table I in the online-only Data Supplement. The mean age of the patients included was 45.3 years (range, 15–87 years) and 60.6% were women.

Quality and Risk of Bias Assessment

Table II in the online-only Data Supplement summarizes the risk assessment using the QUADAS-2 tool for the QUADAS. Overall, there was considerable heterogeneity between studies. There were similarities about the clinical characteristics of included patients: acute headache, normal mental status, no neurological deficit, and similar age and sex distribution. There was significant variation in the incidence of SAH among the studies (Table). Perry et al[11] had low bias risk in the applicability of their study, as they included all SAH-suspected patients presenting to an ED.

The index (gold standard) test was a validated method for diagnosis of SAH including CT or cerebrospinal fluid analysis and clinical follow-up. The index test was applied unevenly across the 5 studies, which could have introduced bias.

The studies by Backes et al,[13] Stewart et al,[18] Blok et al,[20] and Mark et al[29] used medical records review for ascertainment of the cases and follow-up of the cohorts. In the study by Perry et al,[11] patients were identified prospectively the day of the ED visit and then followed by telephone, medical records, review of regional center records, and coroner reports. Any patient who later was diagnosed with an SAH (and survived) would have been transferred to the single regional neurosurgical referral unit. Therefore, unless a patient had a subsequent SAH outside of Ontario, the diagnosis would have likely been captured. We thus considered that the reference standards used in all the studies were appropriate and reproducible.

Outcomes

The studies by Blok et al[20] and Mark et al[29] only included patients with negative CTs, so we estimated their true positives and negatives. Mark et al[29] reported 55 patients with SAH and negative CT and true positives as 1800 patients,[30] with ≈30% having a CT within 6 hours and 11 missed cases of SAH, including 7 patients who had vascular anomalies on cerebral angiography. From the data available, one cannot know if even these 7 patients had true SAH or a thunderclap headache and an incidental vascular lesion on imaging.

The study by Blok et al[20] reports patients with acute headache, and negative CTs per staff radiologist; an LP was performed in all cases. Among the 760 patients with negative CTs, 52 had cerebrospinal fluid positive for bilirubin and only 1 of these was an SAH (a nonaneurysmal, perimesencephalic SAH diagnosed by review of the original CT, which had initially been reported as negative). They did not report the overall incidence of SAH in the cohort so a 2 by 2 table could not be built. We contacted the senior author of this study who communicated that data on SAH incidence or true positive rates were not available in their cohort.

The case definition of a study will greatly influence the incidence. Because Perry et al[11] is the only prospective study performed in EDs, we feel it has the highest potential to be replicated and generalizable. Using the incidence of the Perry

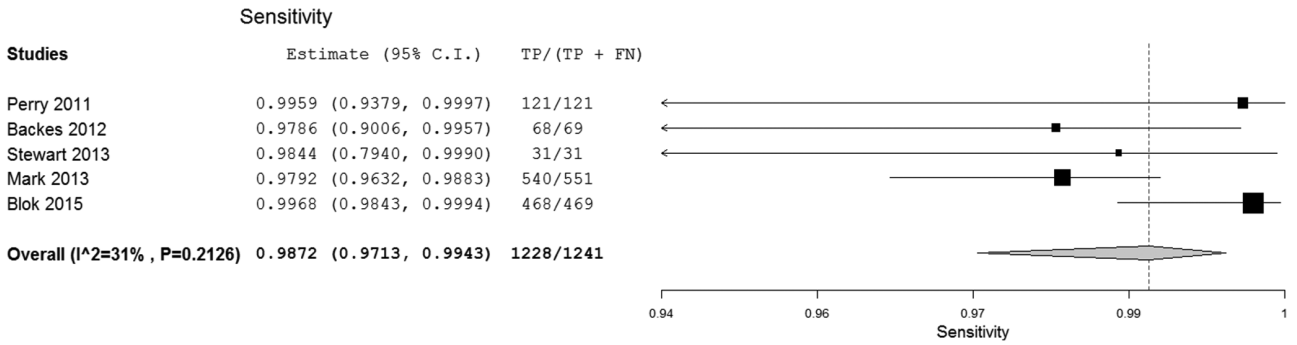

Figure 2. Pooled sensitivity of computed tomographic scan within 6 hours. CI indicates confidence interval; FN, false negatives; and TP, true positives.

et al[11] study (12.7% in the early-presenting group) and the proportion of SAH patients who presented within 6 hours (30%), we estimated a 2 by 2 table for the Blok et al[20] study. Blok et al[20] reported 260 cases of SAH per year and their study period was 6 years, which calculates to 469 SAH among 3600 patients.

Main Results

When all 5 studies[11,13,20,29] were pooled together, we estimated that in the worst-case scenario, 13 of the 8907 patients who underwent CT within 6 hours had a missed SAH (incidence 1.46 per 1000). Overall sensitivity of the CT was 0.987 (95% CI, 0.971–0.994) and specificity was 0.999 (95% CI, 0.993–1.0); Figure 2. The pooled LR of a positive CT was 921.9 (95% CI, 139–6103) and pooled LR of a negative CT was 0.010 (95% CI, 0.003–0.034); Figure 3; Table I in the online-only Data Supplement.

When the study by Mark et al[29] is added with 7 missed cases instead of 11 (those with vascular anomalies on angiography, an intermediate case scenario), the pooled 6-hour sensitivity is 0.989 (95% CI, 0.980–0.994) and the pooled specificity is 1.0 (95% CI, 0.993–1.0).

Sensitivity Analysis

When only the 3 studies[11,13,18] that provide direct information in their 2 by 2 tables are included, the pooled incidence of SAH was 19.1%. One of the 1155 patients who underwent CT within 6 hours of headache onset had a missed SAH. This results in an incidence of missed SAH of 0.87 per 1000 with CT within 6 hours of headache onset. The overall sensitivity of the CT in the 3 studies was 0.986 (95% CI, 0.951–0.996), I^2 0%, specificity 0.996 (95% CI, 0.974–0.999), I^2 28.0%.

Discussion

We found that the CT miss rate of SAH when performed within 6 hours of the onset of headache was <1.5 in 1000 patients. The sensitivity of the CT was 99% and the LR of a negative CT was 0.010. These results suggest that a negative CT within 6 hours may be considered sufficient to rule out SAH in the following circumstances: a neurologically normal patient, a thunderclap headache presentation, a clear time of onset, and a modern CT scan performed within 6 hours of onset read by an attending radiologist.

Our analysis does not apply to patients who present with atypical features (eg, primary neck pain, syncope, or seizure) or any new finding on neurological examination. Such patients do not meet entry criteria for this particular study and the extremely high sensitivity demonstrated here may not apply in these populations.

There are several ways to interpret the data as reported by Mark et al.[29] The most conservative approach is to assume that all 11 cases were true missed SAH (worse case scenario). An intermediate approach would be to assume that only the 7 cases that had associated vascular lesions found were true SAH (intermediate case scenario). Of course, it is possible that even these 7 cases were instances of patients with thunderclap headache and an incidental vascular lesion. Thus to have a conservative approach, we included the study by Mark et al[29] with 11 missed cases (worst-case scenario). It is important to note that for the studies of Mark et al[29] and Blok et al[20] because of the way the data were reported in the articles, we had to estimate certain values to be able to construct a 2 by 2 table using a single prospective study.[11] We think this study is the one that best reflects the patient

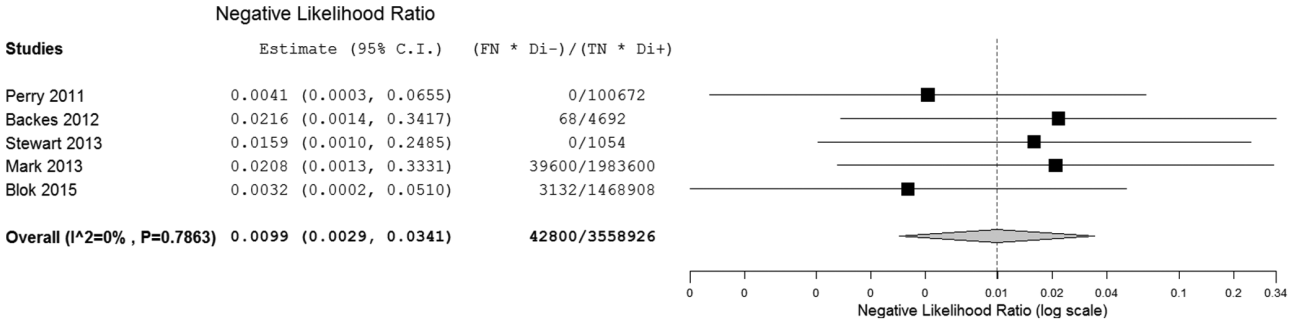

Figure 3. Pooled likelihood ratio of a negative computed tomographic scan within 6 hours. CI indicates confidence interval; FN, false negatives; and TP, true positives.

population to which we will be applying the results of this meta-analysis, as it included a larger cohort and it was a non-referral population.

In addition to these 5 eligible studies, other studies also support the accuracy of CT when performed early after headache onset.[12,14,17,29,31,32] Please see Table III in the online-only Data Supplement. Sidman et al[14] found CT to be 100% sensitive for diagnosing spontaneous SAH if performed within the first 12 hours but did not specify how many of these patients were imaged in the first 6 hours.[19] Bakker et al[17] reported that 94 of 1448 consecutive patients with known SAH were CT negative but LP positive. Of the 12 patients who underwent CT within 6 hours, none had a vascular lesion. Of note, this study defined a positive LP as the presence of bilirubin by spectrophotometry (ie, xanthochromia), which is known to be sensitive but lacks specificity.[33,34]

In an ED population of patients with isolated thunderclap headache who present early enough to undergo CT within 6 hours of symptom onset, the incidence of SAH is reported ≈13% (higher than in patients with thunderclap headache who present later).[11] After a negative CT within 6 hours, the post-test probability decreases to ≤0.2%. The results of our analysis indicate that if one applies this 6-hour rule for CT to diagnose SAH, the worst-case miss rate will be 1 to 2 cases per 1000. The harm from missing these cases must be balanced against the potential consequences of routine LP including time, procedure-related pain, anxiety and complications of LP, unnecessary vascular imaging in the roughly 10% to 15% that have traumatic LPs, and most importantly, the downstream consequences—procedural risks and complications in patients who undergo treatments of incidental vascular lesions, and patient anxiety that having an aneurysm engenders and follow-up imaging for those who do not.[20]

If one were to eliminate the requirement for LP, several important considerations apply (Figure 4). First, our analysis refers only to SAH. Thunderclap headache has a differential diagnosis; if the clinical presentation or epidemiological context suggests another non-SAH diagnosis, further testing beyond CT may be indicated.[2] Second, the sensitivity of CT in this group of patients depends on factors related to the CT scan and its interpretation. In the studies by Perry et al,[11] Stewart et al,[18] and Blok et al,[20] general attending level radiologists read most of the CTs and in the Backes et al[13] study, neuroradiologists interpreted the scans. Trainees and nonexperts have a higher rate of errors in interpretation.[35] In the study by Perry et al,[11] there were 4 instances of scans read as negative by emergency physicians or radiology trainees, and all subsequently read correctly as positive by the attending radiologist.[11] In the studies by Mark et al[29] and Blok et al,[20] some of the scans initially read as negative by general radiologists were later over read as positive.[20,36,37] It is therefore critical that individuals experienced in reading brain CTs interpret the scan and that the clinician clearly communicates the indication for the scan to the radiologist.

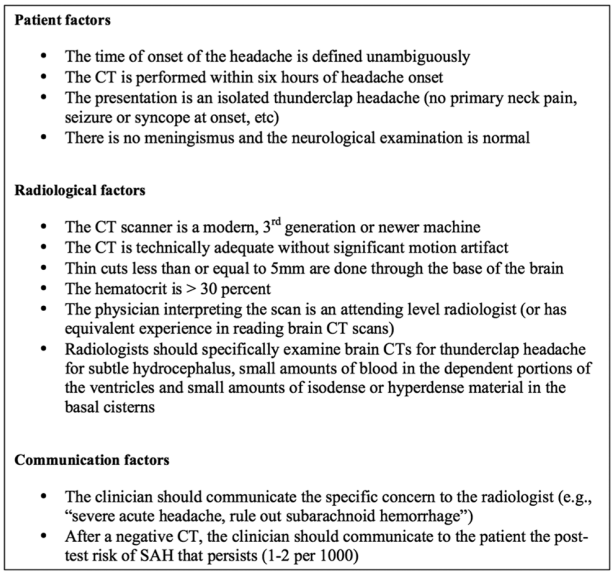

Figure 4. Factors to be considered in applying the 6-hour rule for computed tomography (CT) in subarachnoid hemorrhage (SAH).

Our analysis has several limitations. First, we included only studies involving ED patients presenting with complaints concerning for nontraumatic SAH and with CT scans performed within 6 hours. Because of the clinical heterogeneity of studies pertaining to this topic, only 5 were ultimately included in our meta-analysis. Although the number of included studies is small, we are confident that we included all pertinent studies given the rigor of our search strategy. Second, in the study that contributed the largest number of patients, LP was not performed in all patients, which could have led to overestimation of CT sensitivity.[11] However, the nature of the follow-up in that study (telephonic follow-up, ability to gather information from regional health and coroner records and the fact that the area contains a single regional neurosurgical center) makes this possibility unlikely. Third, the included studies had methodological heterogeneity and have incidences of SAH that seem higher than what is typically seen in clinical practice. Fourth, we recommend to the readers to be careful when evaluating heterogeneity of diagnostic test accuracy reviews relying solely with the I^2, as the included studies differ in the selection of their cohorts and incidences. Finally, the way outcomes were defined and measured (CT only versus CT plus LP) were different. Despite these differences in the definition of the outcomes, we did not see differences in the observed intervention effects. Applying these results to a population with lower prevalence than the one of the included studies increases the negative predictive value, meaning a negative CT is more likely to be a true negative.

Conclusions

In patients presenting with thunderclap headache and a normal neurological examination, a negative brain CT scan within 6 hours of headache onset is highly sensitive in ruling out aneurysmal SAH when the CT scan is technically adequate, and it is interpreted by an experienced radiologist.

Acknowledgments

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Disclosures

Dr Edlow gives expert testimony for cases of neurological emergencies for both plaintiff and defense firms.

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Sensitivity of Early Brain Computed Tomography to Exclude Aneurysmal Subarachnoid Hemorrhage: A Systematic Review and Meta-Analysis

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ONLINE SUPPLEMENT

Sensitivity of early brain CT to exclude aneurysmal subarachnoid hemorrhage: a systematic review and meta-analysis

Nicole M. Dubosh MD, M. Fernanda Bellolio MD, Alejandro A. Rabinstein MD, and Jonathan A. Edlow MD

Supplemental Tables

Appendix: Search Terms

Supplemental References

Table I: 2x2 Table and Likelihood Ratios for Studies Included in Meta-analysis

	TP	FN	FP	TN		Sensitivity	Specificity	LR+	LR-
Perry 2011	121	0	0	832		0.996	0.999	1659	0.00
Backes 2012	68	1	0	68		0.979	0.993	135	0.02
Stewart 2013	31	0	0	34		0.984	0.986	69	0.02
Mark 2013	540	11	0	3600		0.979	1.0	7052	0.02
Blok 2015	468	1	0	3132		0.997	1.0	6246	0.00

Total: 8,907

Abbreviations: TP = true positives, FN = false negatives, FP = false positives, TN = true negatives

Table II: Bias assessment with the QUADAS-2 tool for quality assessment of diagnostic accuracy studies

Study	Year	RISK OF BIAS				APPLICABILITY CONCERNS		
		PATIENT SELECTION*	INDEX TEST†	REFERENCE STANDARD‡	FLOW AND TIMING	PATIENT SELECTION*	INDEX TEST†	REFERENCE STANDARD‡
		Was a consecutive or random sample enrolled? Was case control design avoided? Did the study avoid inappropriate exclusions?	Where the index test results interpreted without knowledge of the results of the reference standard?	Is the reference standard likely to correctly classify the target condition? Where the reference standard results interpreted without the knowledge of the index test?		Are there concerns that the included patients and settings do not match the review question?	Is there concern that the index test, its conduct, or interpretation differ from the review question?	Is there concern that the target condition as defined by the reference standard does not match the review question?
Perry[1]	2011	Low	Low	High	Low	Low	Low	Low
Backes[2]	2012	High	Low	Low	Low	Low	Low	Low
Stewart[3]	2014	High	Low	Low	Low	Low	Low	Low
Mark[4]	2013	High	Low	Low	Low	High	Low	Low
Blok[5]	2015	High	Low	Low	Low	High	Low	Low

* Patient selection: Most studies had an appropriate explanation of the methods for inclusion and had consecutive patients. Biases are introduced in case control studies, as including participants with known disease and a control group without the condition exaggerate diagnostic accuracy. The inclusions were appropriate, however the exclusions were different between studies.

Because most studies included confirmed cases of SAH, the incidence of disease and sensitivity will be higher than in studies with patients with suspicious for SAH.
Applicability of patient selection refers to concerns that the included patients and setting do not match the review question. In this review, there are biases on patient selection that affect the applicability. The incidence of SAH is significantly higher in the included studies when compared to what we see in clinical practice of undifferentiated acute thunderclap headache so there is concern in all of the studies. Perry et al is the only one that included suspicious of SAH and is more likely to reflect our practice. All the studies aim to evaluate the sensitivity of CT within the first few hours of SAH.
†Index Test: The retrospective and chart review methodology could have introduced biases to the index test. False positives were not measured in most studies and are difficult to determine clinically in cases of SAH (ie: is the aneurysm incidental or ruptured?), however all of the patients had their CT initially interpreted in real time by a radiologist, so we assigned low risk of biases in this category to all studies.

‡Reference standards assume that there is one gold standard. We compared CT to CT/LP/follow up as final diagnostic. There was difference in the method of follow up as well as the number of patients with LP in different studies.

Other biases: Time span of Mark study is 2000 to 2011, and this could have introduced bias in CT image quality, as modern scanners differ from early 2000's CTs.

Table III: Additional studies evaluating the diagnostic value of early CT scan for the diagnosis of SAH but not meeting our entry criteria

Study	**Type/Setting**	**Findings**	**Reason for exclusion from meta-analysis**	**Additional comments**
Van der wee, 1995[6] n = 175	Prospective	2% miss rate of noncontrast head CT alone in detecting SAH if performed within 12 hours	Data for patients scanned within six hours not specified	
Sidman, 1996[7] n = 140	Retrospective	100% sensitivity of third generation noncontrast head CT if performed within 12 hours	Data for patients scanned within six hours not specified	
Byyny, 2008[8] n = 149	Retrospective	93% sensitivity of noncontrast head CT for detecting SAH	Time of CT scan not specified	
Lourenco, 2009[9] N = 61	Retrospective	97% sensitivity of noncontrast head CT for detecting SAH	Data for patients scanned within six hours not specified	One patient missed was imaged 10 hours after time of onset
Bakker, 2014[10] n = 1448	Cohort, prospective	100% sensitivity of noncontrast head CT if performed within the first 6 hours	Patient population (only analyzed CT negative patients in a cohort of patients with SAH)	12 patients imaged within 6 hours with (-) noncontrast head CT, (+)LP, 0 found to have vascular lesion.

Abbreviations: ED = emergency department, HA = headache, SAH = subarachnoid hemorrhage, LOC = level of consciousness, LP = lumbar puncture

WEB-ONLY APPENDIX: SEARCH TERMS

PubMed
headache* AND (sah OR hemorrhage, subarachnoid[mesh] OR "subarachnoid hemorrhage*" OR "subarachnoid haemorrhage*") AND (emergenc* OR emergency service, hospital[mesh] OR early OR hours) AND (ct OR cat OR tomogr*) 273

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present

#	Searches	Results	Search Type
1	sah.mp. or subarachnoid hemorrhage/di, ra or "subarachnoid hemorrhage*".mp. or "subarachnoid haemorrhage*".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	23922	Advanced
2	(headache* or thunderclap*).mp. or headache disorders, primary/di, ra [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	68610	Advanced
3	emergenc*.mp. or emergency service, hospital/ or ed.tw. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	305777	Advanced
4	("predictive value" or sensitiv* or "confidential interval*" or rules or "false negative" or "rule out" or reproducib*).mp. or diagnostic support techniques/ [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	1654694	Advanced
5	1 and ((ct or cat or tomogr*).mp. or exp tomography, x-ray, computed/) [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	5863	Advanced
6	5 and (3 or emergency medical service/ or early.mp. or early diagnosis/ or timing.mp. or time factors/ or six.mp. or "6".mp. or hours.mp. or hrs.mp. or day.mp. or days.mp. or "h".mp.)	3052	Advanced
7	4 and 6	472	Advanced
8	5 and headache*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	1001	Advanced
9	3 or emergency medical service/ or early.mp. or early diagnosis/ or timing.mp. or time factors/ or six.mp. or "6".mp. or hours.mp. or hrs.mp. or day.mp. or days.mp. or "h".mp.	5715208	Advanced
10	8 and 9	538	Advanced
11	7 or 10	936	Advanced
12	11 and ("case series" or "case control*" or cohort* or prospective* or retrospective* or sensitiv*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	433	Advanced
13	remove duplicates from 12	419	

Embase 1988 to 2015 Week 16

#	Searches	Results	Search Type
1	subarachnoid hemorrhage/di [Diagnosis]	4770	Advanced
2	tomography/ or brain tomography/ or computer assisted tomography/	467920	Advanced
3	1 and 2	2567	Advanced
4	limit 3 to human	2525	Advanced
5	exp emergency medicine/ or exp emergency patient/ or exp emergency care/ or exp emergency ward/ or exp emergency health service/	149288	Advanced
6	4 and (5 or emergen*.mp.) [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	335	Advanced
7	4 and headache*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	772	Advanced
8	*subarachnoid hemorrhage/di and 4	1441	Advanced
9	diagnostic accuracy/ or diagnostic test accuracy/ or diagnostic value/	275061	Advanced
10	predictive value/ or "rule out".mp. or "ci".mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	438938	Advanced
11	8 and 10	74	Advanced
12	8 and 9	138	Advanced
13	8 and negative.mp. and positive.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	39	Advanced
14	(6 or 7 or 8) and ("sensitivity and specificity"/ or predictive value/ or "false positive".mp.) [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	95	Advanced
15	exp case control study/ or exp case study/ or exp clinical trial/ or exp "clinical trial (topic)"/ or exp intervention study/ or exp major clinical study/ or exp prospective study/ or exp retrospective study/	2875138	Advanced
16	(6 or 7 or 8) and 15	452	Advanced
17	(6 or 7 or 8) and (observational* or cohort* or prospective* or retrospective*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	272	Advanced
18	(6 or 7 or 8) and (early* or "6" or six or hours or hrs or day*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	684	Advanced
19	(12 or 13 or 14 or 16 or 17) and 18	305	Advanced
20	11 or 12 or 13 or 14 or 16 or 17 or 19	618	Advanced
21	remove duplicates from 20	616	Advanced
22	21 not (case report/ or short survey.pt. or conference report.pt. or editorial.pt. or trade journal.pt.)	551	Advanced
23	limit 22 to embase	537	Advanced

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Abstract

動脈瘤性くも膜下出血の除外に対する早期脳 CT の感度

―系統的レビューとメタアナリシス

Sensitivity of Early Brain Computed Tomography to Exclude Aneurysmal Subarachnoid Hemorrhage

A Systematic Review and Meta-Analysis

Nicole M. Dubosh, MD[1,2]; M. Fernanda Bellolio, MD[3]; Alejandro A. Rabinstein, MD[4], et al.

[1]Department of Emergency Medicine, Beth Israel Deaconess Medical Center, Boston, MA; [2]Department of Emergency Medicine, Harvard Medical School, Boston, MA; [3]Departments of Emergency Medicine and [4]Neurology, Mayo Clinic, Rochester, MN

背景および目的：早期に施行する脳 CT の高い感度を証明するエビデンスが増加しつつあり，自然発症くも膜下出血（SAH）の診断において CT 陰性後に常に腰椎穿刺を施行する必要性に関して疑問が生じている。本研究は，神経学的所見が正常な患者において，頭痛出現から 6 時間以内に最新の撮影装置（16 スライス以上）を用いて撮像した脳 CT の SAH の除外に対する感度を検討することを目的とした。

方法：Ovid MEDLINE，Ovid EMBASE，Web of Science，Scopus を用いた包括的な文献検索を行い，メタアナリシスを実施した。自然発症 SAH に関連する既往歴があり，発症後 6 時間以内に新世代のマルチスライス CT 装置を用いて撮像された非造影脳 CT が得られている成人に関する原著調査論文を解析対象とした。本研究は，preferred reporting items for systematic reviews and meta-analyses（PRISMA）を遵守している。

結果：合計 882 件の表題を調査し，推定 8,907 例の患者を対象とする 5 件の論文が採用基準を満たした。13 例で 6 時間以内に施行された脳 CT で SAH が見逃されていた（発現率 1.46/1,000）。CT の全体的感度は 0.987［95％信頼区間（CI）：0.971 ～ 0.994］，特異度は 0.999（95％ CI：0.993 ～ 1.0）であった。CT 陰性の統合した尤度比は 0.010（95％ CI：0.003 ～ 0.034）であった。

結論：雷鳴頭痛を呈するが神経学的所見が正常な患者において，頭痛出現から 6 時間以内に施行された脳 CT での正常所見は動脈瘤性 SAH を除外するうえで極めて感度が高い。

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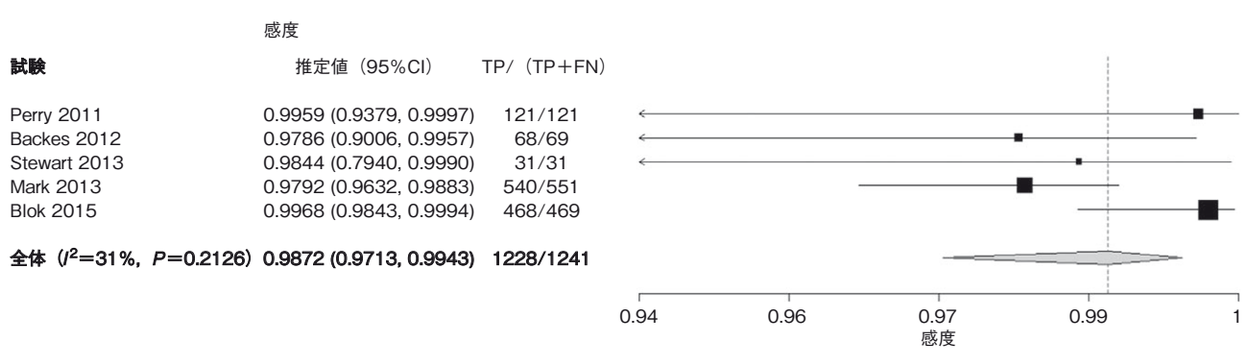

図 2 6 時間以内に施行した CT の統合した感度。CI：信頼区間，FN：偽陰性，TP：真陽性。

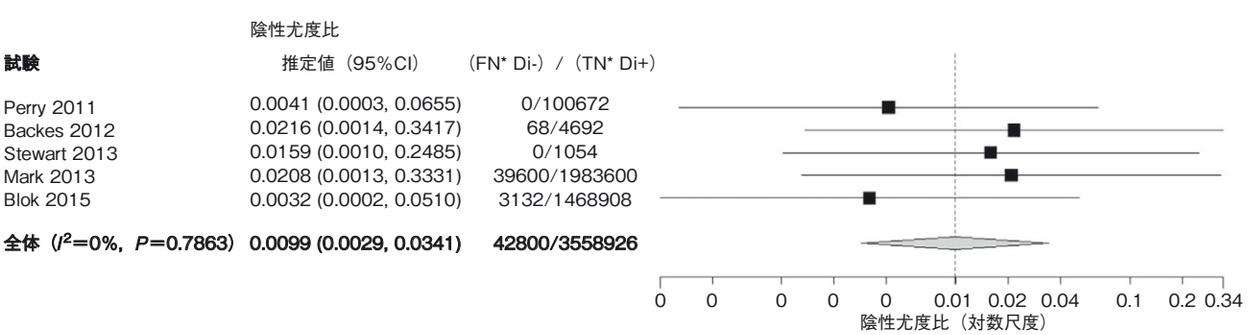

図 3 6 時間以内に施行した CT 陰性の統合尤度比。CI：信頼区間，FN：偽陰性，TP：真陽性。