# How Good Is a Negative Cranial Computed Tomographic Scan Result in Excluding Subarachnoid Hemorrhage?

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## CLINICAL SCENARIO

A 45-year-old woman presents to your community emergency department at 10 PM on a Friday, complaining of a headache. She is able to relate her current symptoms and past experience with headaches lucidly and consistently. She describes the rapid onset of a severe (rated 8 on a scale of 10) bitemporal and vertex headache that began at noon that day, reaching peak intensity within 2 minutes, while she was lying on the couch watching television. She took 1,000 mg of acetaminophen with partial temporary relief, and felt well enough to have a sandwich for lunch. She has had nausea but no vomiting. She has frequent "tension" headaches that, on rare occasions, have been equally bad, but this headache feels distinctly "different."

She denies recent head injury, fever, visual symptoms, neck pain or stiffness, abnormal sensation or strength, and chest or back pain. She has mild hypertension treated with atenolol, does not smoke cigarettes, and drinks alcohol socially. There is a family history but no personal history of migraine.

On physical examination, she is afebrile with a blood pressure of 140/88 mm Hg and a normal pulse and respiratory rate. She is awake, alert, and conversational but appears uncomfortable. Her general physical examination is entirely normal. The neck is supple; there is neither meningismus nor other signs of meningeal irritation. A thorough neurologic examination, including assessment of the optic fundi, visual fields, gait, and mental status, is also normal.

The history of a relatively abrupt onset of severe headache that is "different" from previous episodes raises the possibility of an aneurysmal subarachnoid hemorrhage (SAH). Against this diagnosis are the findings that the

headache is not the "worst of her life," began at rest, partially responded to a nonnarcotic analgesic, and that her physical examination yields normal findings. Nevertheless, you are concerned that she might have an SAH and explain this to the patient.

You suggest to her that in your judgment, based on your knowledge of the literature,[1,2] she has, at most, a 15%, or 1 in 6, chance of having an SAH and that the first step in the evaluation is a cranial computed tomographic (CT) scan. If the scan shows blood, you will consult a neurosurgeon. You further explain that if the result of the CT scan is negative, then she should undergo a lumbar puncture (LP) because the CT scan is not 100% sensitive for blood and because of serious consequences of a missed diagnosis of SAH. The patient is concerned about the LP as she developed a severe headache after a "spinal" anesthesia 20 years ago. She wants to know her chance of having the SAH if the CT scan result is negative. You ask her, "How low would the likelihood have to be for you to choose not to have the LP?" She thinks for a moment and then replies, "It would have to be very low, perhaps 1 in a 100." After further discussion, the patient wants another opinion about the need for the LP. She agrees to the CT scan and you agree to consult a colleague.

Your colleague tells you that because the duration of the headache is less than 12 hours and because the hospital uses a third-generation CT scanner, a negative scan result is sufficient to exclude SAH. You counter that your training dictated that all patients with negative CT findings should undergo LP to exclude SAH. You and the patient agree to talk again after the scan, which will be interpreted by an attending general radiologist. Meanwhile, you decide to review the literature with the online search software at your disposal on the Internet.

Throughout the rest of this installment, the authors will lead the reader through a systematic process of evaluating this clinical dilemma. We begin by figuring out how to best formulate the question. We then describe an appropriate approach to searching for the best evidence. Finally, we lead the reader through the process of analyzing it and applying it to clinical practice. In the course of this process, we will resolve the scenario and propose "conclusions" consistent with the scope of this review.

## FORMULATING THE QUESTION

To be able to perform an efficient search, one must first clearly define the question. There are many questions that arise regarding diagnostic strategies for patients with suspected SAH, such as, "Is an LP, as a first diagnostic test, a safe and effective strategy?" However, the question that you are concerned with here pertains to the need for further testing when an initial CT scan yields a negative result.

There are 4 components that help to frame a question about a diagnostic test—the population to be tested, the test used, the criterion standard against which the test is to be measured, and the ability of the results of the test to rationally guide changes in clinical decisionmaking. When the test is being used to alter a preestablished clinical estimate of the patient's likelihood of disease (the pretest probability), the last component translates into the clinical importance of the revised estimate that follows from the result of the test in question (the posttest probability).

In our case, the patient population of interest is fairly clear. You are concerned about adults with severe, acute-onset headache who present on an emergency basis to an ED or other ambulatory setting. Furthermore, these patients must have a normal neurologic examination including normal mental status and no meningismus. Another important factor is the duration of time from onset of headache to obtaining the CT scan because the sensitivity of CT scanning decreases as this interval increases, being the highest within the first 12 to 24 hours after onset of headache.

This element of time, especially germane to emergency medicine, may be considered a special case of the population to be tested. That is, the performance of the same diagnostic test in the same population may be dramatically different as a function of time. An example familiar to emergency physicians is determination ofr creatine phosphokinase levels in patients with suspected acute myocardial infarction. In our example, the patient population needs to be further refined to that subset of patients presenting within 12 hours of onset of headache.

The test to be examined is the cranial CT scan—specifically, a modern third-generation scanner—performed without contrast. These scanners are defined by a cylindrical x-ray tube with an array of detectors mounted along a portion of the same tube, which rotates around the patient. For the moment, you will set aside the issue of who is interpreting the scan. Specifically, you are interested in the negative CT scan result. That is, you are not concerned about the possibility that a scan interpreted as "positive" by the radiologists would be later shown to have been a false-positive reading. In the appropriate clinical setting, if a scan is interpreted as positive for blood in the subarachnoid space, most practitioners would be entirely

comfortable proceeding to the next stage of specialty evaluation.

The next issue is to determine the criterion against which the CT scan result is to be gauged. This is sometimes referred to as the gold standard or reference standard. The possibilities include LP, clinical follow-up, angiography, and surgical exploration. The latter 2 interventions are almost never performed in patients with negative findings on CT scans and clear cerebrospinal fluid (CSF). Therefore, practically speaking, it is unlikely that you will find a study that uses them as a criterion standard. The LP is recommended by most physicians in the situation of a patient with an acute, severe headache, normal neurologic examination, and normal CT findings.[3-6] The CSF is examined for blood and xanthochromia. Ideally, you would like to see a study that performs LP in all patients being evaluated for SAH—those with both negative and positive CT scan findings. However, in reality, because of the practice convention alluded to above, you think it unlikely that you will find a study in which LP has been performed on all patients with positive scan results. Recognizing the problems with traumatic LPs, you nonetheless decide that LP is the practical and clinically relevant criterion to use for identifying the presence or absence of SAH in patients whose CT scans are interpreted as negative.

The CSF findings that are considered positive for SAH are usually limited to xanthochromia and the presence of constant amounts of RBCs from the first to the last tubes. However, various investigators use different methods of determining the former, and there is no specific cutoff of number of RBCs that rules in or rules out SAH.[7] Although xanthochromia may take up to 12 hours to develop in some cases, all of these early cases show bloody CSF. Therefore, finding normal CSF, even in the first hours after onset of headache, does exclude SAH. It is possible for bloody CSF to not yet be xanthochromic in the first 12 hours after hemorrhage. One recent review recommended that LP not be delayed and that finding either RBCs or xanthochromia should mandate vascular imaging.[3]

There are several assumptions inherent in this logic. First, you are assuming that patients with positive findings on CT scan have true SAH. The premise is to accept a final positive CT reading as truly positive. This is the way clinicians operate in the real world, despite confusion that might occur in rare individual cases. Additionally, you are assuming that patients with both negative CT scan findings and negative LPs do not have SAH. This is certainly the standard of practice and there is literature to support it. Three studies have followed clinical outcomes in patients with "thunderclap" headache and negative CT scan and LP findings. None of the patients subsequently developed SAH.[8-10] The largest of these retrospectively examined the outcomes of 71 such patients for an average of 3.3 years.[10] The outcome you are interested in, and the question that your patient has posed to you, is how likely is SAH when a state-of-the-art CT scan yields negative findings within 12 hours of onset of symptoms. Specifically, the outcome of interest in this scenario is the ability of a negative CT scan result to sufficiently lower the likelihood of SAH in a patient with a relatively low clinical suspicion. As elucidated in a previous article in the evidence-based emergency medicine series,[11] the test characteristic that will be most helpful in assessing this will be the likelihood ratio for a CT negative result for subarachnoid blood in patients undergoing evaluation for SAH.

Most clinicians and patients would require that the likelihood of SAH be exceptionally low at the point that further evaluation would be deferred for an individual patient. This is because untreated SAH carries a very poor prognosis.[4,12] Approximately 60% to 70% of patients either die or suffer serious neurologic disability. One important cause of this morbidity and mortality is early rebleeding.[4] In a patient presenting in good clinical condition with a "sentinel" hemorrhage, subsequent rebleeding often results in death or severe neurologic disability.

Furthermore, effective therapy exists for patients who present in good clinical condition, whose condition is diagnosed correctly, and who are treated promptly. These patients have an excellent prognosis. Because an LP (especially after a negative CT scan) is a safe, relatively inexpensive test, most clinicians would require that the patient have an extremely low posttest probability of SAH after negative CT findings if they were to feel comfortable not performing an LP.

Therefore, further questions include: What is the threshold needed to stop the evaluation after a negative CT scan result?[11] How low does the posttest probability become after negative CT findings? Is this level of risk acceptable to you as a clinician? Because the patient understands the issues and wishes to be part of the decisionmaking process, an equally, if not more important question is, "Is this level of risk acceptable to the patient who prefers not to undergo an LP?"

The reformulated summary question for our patient is "Does a negative result of a noncontrast CT scan performed on a third-generation machine within 12 hours of onset of headache reduce the likelihood of SAH to below 1% in

adult patients presenting to an ED with acute, severe headache and a normal neurologic examination?"

## SEARCHING AND SELECTING THE BEST EVIDENCE

The MEDLINE database includes all journals in *Index Medicus* from 1966 to the present and currently comprises approximately 4,300 biomedical journals indexed by the National Library of Medicine in Bethesda, MD. Because your hospital provides Internet access, you have the ability to search this database free of charge via PubMed.

When a busy clinician performs a MEDLINE search for literature relevant to a particular clinical question, he or she must be prepared to decide which of a potential multitude of citations located are most likely to be useful in clinical decisionmaking. When a researcher embarks on a formal review of a clinical topic, she or he must decide beforehand on the characteristics of the articles ultimately selected for inclusion in the review. As a clinician, you may be unaccustomed to writing a list of criteria that you intend to use to select articles in advance of a literature search. On the other hand, you do not read every study. You make judgments, sometimes intuitively, other times consciously, as to which articles will best help answer the question that led to the search in the first place. To move beyond an intuitive approach, with its inherent risk of bias, you are best advised to determine in advance the selection criteria that are most likely to lead to the articles that will best answer the question you have posed.

Appropriate criteria that might be used in connection with the search for relevant studies on CT scans in the diagnosis of SAH include prospective primary investigations, as opposed to editorials, reviews, or letters to the editor. Type of scanner used, spectrum of disease in the population studied, and time window of the evaluation are others. You are only interested in studies using modern, third-generation CT scanners because earlier-generation CT technologies might perform differently with respect to the diagnosis of SAH. Most hospitals in North America have been using third-generation scanners since the mid-1980s. Therefore, you decide to limit the search to articles published from January 1985 through March 2000. Clearly, the articles that you will choose must be relevant to the population that you see in your practice—adult patients presenting to the ED with severe, acute-onset headache, often referred to as the "worst headache of life," with no neurologic deficits on physical examination. Furthermore, data must be presented on those patients who have presented within 12 hours after the onset of their headache. It will be important that the study population include subjects for whom the clinical estimate of risk lies within the lower end of the spectrum of patients for whom SAH is considered the principal diagnosis to be excluded. Because a CT scan might well perform better on high-risk than low-risk patients, you will be reluctant to extrapolate the results of a study done on the former to the clinical decisionmaking regarding the latter. The ideal study design would be a prospective, consecutive series of ED patients. Such a study design would maximize the ability of the investigators to correctly identify and characterize the clinical characteristics of the study population. For practical reasons, you decide to limit your search to articles published in the English language.

Beyond this, it will be important to know how the diagnosis of SAH was ultimately established or rejected; that is, what criterion standard was used? As noted, all the patients with negative CT scan results will need to undergo LP if the data are to be useful. Because of the considerations elaborated in the preceding section, you elect to waive what would, under most circumstances, be considered a "bottom line" requirement for a study of predictive power of a diagnostic test—that is, that an acceptable criterion standard be applied in a blinded fashion to all subjects receiving the test under evaluation. You will not require that positive CT scan findings among subjects being considered for possible SAH be verified through an independent test. In other words, you will assume, for purposes of your review, that the CT scan is 100% specific (ie, no false-positive results) for the diagnosis of SAH under the clinical circumstances at hand. In summary, appropriate inclusion criteria would be studies of adult ED patients being evaluated for SAH who present within 12 hours of onset of symptoms and on whom a third-generation CT scan has been done on all patients and an LP has been done on all patients with negative CT findings.

Using PubMed, you begin by searching the last 15 years using major medical subject heading (MeSH) terms (January 1985 to March 2000). You enter "subarachnoid hemorrhage" AND "tomography, x-ray computed" AND "spinal puncture." Also, because the term "spinal puncture" is infrequently used, you add "lumbar puncture" OR "spinal fluid" as text word alternatives. This search yields 84 articles. By visually scanning the titles and abstracts, you reject 80 of them for various reasons (Table 1), leaving 4 articles for consideration. Examining the reference lists of these articles does not identify any other articles that appear useful. Although only 1 of the 4 studies in-

volved a primary ED population, it did not, strictly, report data on patients presenting within 12 hours of symptom onset. You therefore decide, preliminarily, to look at the results of all of them for the purpose of determining the range of CT sensitivities observed in more or less selected populations.

MEDLINE is not your only source of information. From periodic scanning of the literature, you are aware of a recent review of evaluation of headache that the MEDLINE search failed to identify.[14] You review the extensive bibliography of that article to ensure that you have not missed any important studies, and do not find any that meet the criteria for your search.

## ANALYZING THE EVIDENCE

Although the 4 selected articles all address the basic question of the sensitivity of modern CT scanning in patients in whom SAH is suspected, they are not equivalent studies. Each has limitations. The first important issue to consider is their validity.

The assumptions that have been made in the process of formulating the question have categorically rendered 2 of the validity criteria nonapplicable. As expected, none of the studies involved a systematic performance of LP on all patients considered for the possibility of SAH irrespective of the results of the CT scan. Strictly speaking, this means that a criterion standard was only applied to patients whose CT scans were interpreted as negative and not to those with positive scan results. You will therefore have to give some consideration to the possibility of false-positive CT scan results in looking at the results of the studies you have selected. You do not find any data about interobserver variability in CT readings for SAH or about any objective criterion with which to compare 2 interpretations of the same scan in the studies you have selected. It is important to acknowledge that, in the absence of uniform application of an independent criterion standard, any significant variability in CT interpretation challenges the assumption of 100% specificity in the scan.

It is also important to acknowledge that the decision to perform the LP was not independent of knowledge of the CT results. In addition to the issue of false-positive CT scan results, this raises the possibility of whether the clinician's awareness that the CT result was negative might have biased the interpretation of the LP. However, laboratory technicians who are unaware of the CT scan results usually determine xanthochromia and RBC counts and spectrophotometric assays for xanthochromia are observer independent. It is therefore unlikely that the lack of independence between these assessments constitutes an important source of bias in these studies.

Although the question of false-positive CT findings must be considered, the assessment of validity of the studies you have selected will center on the appropriateness of the patient spectrum and the precision with which the tests in question, CT scan and LP, are described. Of these, spectrum is by far the most important issue.

Reading the methods section of any scientific article is crucial. Among other things, when a diagnostic test is involved, you want to be certain that the patient population studied by the investigators matches as closely as possible the patient(s) for whom you are likely to order that test. A test such as CT scan, as an indirect measure of blood in the subarachnoid space, may perform better on patients admitted to a neurosurgical unit or those with large hemorrhages, than it does on awake and alert patients presenting to an ED with headache. This potential for bias is known as spectrum bias. In particular, you would expect CT to likely have a higher sensitivity on the former population than on the latter.[16] In fact, this was exactly the case in the International Collaborative Study on aneurysms, in which alert patients with SAH were more likely to have negative CT scan results than patients with neurologic abnormalities (although this was partly attributable to later presentation in the alert patients).[17,19] When you examine the spectrum of patients in the 4 articles you have selected, you find a wide range.

An important indicator of the diagnostic spectrum included within a study population is the percentage of patients who "ruled in." The articles by Sidman et al[19] and

**Table 1.**
*Search strategy and results.*

| Search Terms/Strategy | | No. of Studies |
|---|---|---|
| "Subarachnoid hemorrhage" [MeSH] AND "Tomography, x-ray computed" [MeSH ] AND {"Spinal puncture" [MeSH ] OR "lumbar puncture" [text word] OR "spinal fluid" [text word]} | | |
| Limited to articles published between 1/1/85 and 3/10/00 | | 84 |
| **Reason for elimination of articles** | | |
| Based on review of citations | | |
| Subject not relevant | 43 | |
| Foreign language | 23 | |
| Case reports, letters, reviews, editorials | 11 | 77 |
| Subtotal | | 7 |
| Based on review of abstracts | | |
| Unrelated to question | | 3 |
| Considered in review[2,19-21] | | 4 |

Sames et al[20] examined patients admitted to the hospital with SAH identified retrospectively by *International Classification of Diseases, ninth revision,* codes. In these studies, because only patients who "ruled in" for SAH were included, the overall severity and risk of SAH within the population from which they were drawn cannot be known. Another clue to the study spectrum is the disease severity within the included patients. In the former study, which describes the Hunt and Hess scores (a widely used scoring system for severity of SAH), 39 (48%) of the 80 patients who had CT scans within 12 hours had focal deficits or mental status changes, a significant difference from your low-risk patient. Furthermore, and perhaps more to the point, neither of these studies address the sensitivity of CT in awake, neurologically intact patients who present to the ED with headache. Therefore, you decide to eliminate these 2 studies from further consideration. Table 2 summarizes the details of the remaining 2 studies.

The study by van der Wee et al[21] describes patients with acute headache who were oriented and had no focal neurologic findings. The authors do not specify what proportion of the patients had meningismus. In this study, patients were admitted to the hospital and had LP deferred by at least 12 hours after onset of headache. Sixty-eight percent of the patients had SAH, a proportion far higher than the pretest risk you had assigned to your patient and higher than that reported in the prospective study done in a US hospital. Although the authors state that patients were "oriented" and had no focal neurologic deficits, more detailed information on the clinical characteristics, such as the results of more detailed mental status and cognitive evaluations, would be needed for you to be sure that the high rule-in rate did not reflect an inappropriate spectrum of disease. The authors also do not define hospital admission criteria. The remaining study, by Morgenstern et al,[2] most closely approximates a population conforming to the characteristics of your patient. Outpatients with severe headache (although even in this study, only patients with "worst headache of life") were included and meningismus was not an exclusion criterion.

The time horizon examined differed in the 2 studies; the study by van der Wee et al[21] used a 12-hour window and that by Morgenstern et al[2] reported on patients who had scans up to 24 hours after onset of symptoms. However, Morgenstern et al do report that the 1 patient who had a false-negative CT scan in the group presenting within 24 hours actually presented 1 hour after onset of

**Table 2.**
*Characteristics of the selected articles.*

| Study Characteristic | van der Wee et al[21] | Morgenstern et al[2] |
|---|---|---|
| Study design | Retrospective review—consecutive patients | Prospective study |
| Patient population | 175 admitted patients with acute headache presenting ≤12 h of symptom onset, oriented, and no focal neurologic findings (meningismus not commented on) | 41 of 51* adult ED patients with worst-of-life headache, no neurologic findings (meningismus allowed), and presenting ≤24 h of symptom onset<br>Exclusion criteria: head trauma within past 3 months, LP within prior 2 weeks, coagulopathy or platelets <50,000, temperature >38.5°C, head CT scan showing mass, edema or intracerebral hemorrhage, cancer, focal neurologic signs (except photophobia or meningismus) |
| Pretest risk (% of population with SAH) | 68% | 17% (of enrolled patients)<br>11.8% (of eligible patients) |
| Setting | Netherlands | USA |
| CT scanner used | Third-generation (GE model 9800 Hi-Lite Advantage) scanner | Third-generation (Philips Tomoscan 350 or 500) scanner |
| Scanning protocol | Contiguous 3-mm cuts through basal cisterns<br>Noncontiguous 5-mm cuts in higher regions | 5-mm cuts through posterior fossa<br>10-mm cuts above |
| Criterion standard | LP: xanthochromia by spectrophotometry | LP: RBC count >1,000 (and no decrement >25% from first to last tube) AND (xanthochromia, either visual or by spectrophotometry, OR positive D-dimer assay result) |
| Time cutoff used | 12 h | 24 h |
| Who interpreted the scans | Joint reading by a neuroradiologist and 2 neurologists, all experienced in SAH | 2 neuroradiologists |
| Interobserver variability in CT scan interpretation | NR | NR |

**NR,** Data not reported in the article.
*Ten enrolled patients refused LP. The time from onset of symptoms is not reported for these patients.

symptoms. You believe it very unlikely that patients whose scans were positive for blood later than 12 hours but less than 24 hours after symptom onset would have had a negative scan result earlier. Therefore, the less-than-24-hour group in the Morgenstern et al study may in fact be taken as the equivalent of a less-than-12-hour group for the purpose of the question you have asked. In summary, the study by Morgenstern et al comes the closest to fulfilling your prespecified inclusion criteria.

How does one proceed when the relevant studies on a question have important shortcomings? The first step in such a situation is to determine whether the direction of effect of potential sources of bias on the results is predictable. It was noted above that a spectrum bias in the direction of higher-risk patients for SAH could reasonably be expected to enhance the apparent sensitivity of the CT scan for subarachnoid bleeding. Taking note of such a bias, if you then find that the sensitivity of the scan for this population is not acceptable, you will be even firmer in your resolve not to accept the results of a negative scan without further corroboration by means of an LP. If, on the other hand, the CT scan for the high-risk group was 100% sensitive, the inappropriate spectrum will result in significant doubt regarding the conclusion that the likelihood of SAH has been adequately reduced in your lower-risk patients. You will need data from an appropriate study population to erase this doubt.

The second step is to determine whether a given study has multiple sources of potential bias likely to have either conflicting or unpredictable effects on the observed results. In such cases, the overall impact of the biases on our conclusions may not be predictable. In this eventuality, the remaining recourse is to determine whether individual studies using different methodology actually observed different results (ie, was there an impact of study quality on the observed sensitivity of CT for SAH?).

Neither article directly reports likelihood ratios (LRs), so you calculate them using a formula provided in a previous article in the *Annals* evidence-based emergency medicine series about their use in clinical decisionmaking,[11] and following your assumption of 100% specificity for CT (Table 3). This assumption makes calculating the LR easier, because the denominator will be 1 in each case (Figure).

## APPLYING THE EVIDENCE

Will this evidence help you and your patient make a more informed decision? There are several factors to consider. First, is the diagnostic test, cranial CT scan, sufficiently described so as to permit replication in your hospital? The answer here is affirmative. The scanner in your hospital and the protocol used are very similar to what was used in the various studies.

**Table 3.**
*Performance of third-generation CT scan in the 2 included studies.*

| Characteristic | Morgenstern et al[2] | van der Wee et al[21] |
|---|---|---|
| No. of patients presenting <24 h | 41/51* | 175 |
| No. positive for SAH | 15 | 119 |
| No. with CT scan result positive for blood | 14 | 117 |
| CT scan result negative for blood/LP negative | 36 | 56 |
| CT scan result negative for blood/LP positive | 1 | 2 |
| LR for CT scan result to be negative for blood† | 0.07 | 0.02 |
| 95% CI for negative LR‡ | 0.01, 0.4 | 0.004, 0.07 |

*Ten enrolled patients in the study refused LP. The authors do not report how they were distributed between the groups presenting less than or more than 24 hours within onset of symptoms.
†LRs for negative CT scan results were calculated as the percentage of patients with SAH missed by CT scan divided by the percentage of patients without SAH who had negative CT scan findings.
‡Calculated using the University of British Columbia's free posted "Bayesian Calculator," available at: http://www.healthcare.ubc.ca/calc/bayes.html.

**Figure.**
*Calculation of LRs for a negative test result when the criterion standard is only performed on patients with a negative index test.*

| | Subarachnoid Hemorrhage | |
|---|---|---|
| **Third-Generation CT Scan Result** | **Present** | **Absent** |
| Positive | a | b |
| Negative | c | d |

- All patients with a positive test result (CT scan) are assumed to have a true positive result. Hence, b is 0 as an assumption.
- The LR for a negative test result (CT scan) is the percentage of patients who are judged to have the disease (SAH) who have a negative scan result divided by the percentage of patients who are judged *not* to have the disease who have a negative scan result.
- The percentage of patients with SAH who have a negative CT scan result=c/a+c.
- The percentage of patients without SAH who have a negative CT scan result=d/b+d.
- Because b≡0 by assumption, d/b+d≡1 by assumption.
- Therefore, the LR for a negative index test=c/a+c.
- Calculation of CIs around this LR requires the use of all exact numbers for a, b, c, and d.

Regarding the next step, interpretation of the scan, you feel on less firm ground. In both studies, neuroradiologists interpreted the scans, in 1 case, jointly with 2 neurologists experienced in evaluation of SAH. You are aware of literature that shows significant variability in physicians' ability to accurately interpret cranial CT scans in patients with acute stroke, even those with hemorrhagic stroke.[22] In that study, a minority of emergency physicians and neurologists and only 52% of the board-certified general radiologists correctly identified all the hemorrhages. This study did not include patients with SAH.

Neither study that you have selected reported on interobserver variability. You are therefore concerned about the external validity of these studies to a community hospital without a trained neuroradiologist. This particularly concerns you because, if just a few patients whose results were interpreted as positive by a trained specialist were interpreted as negative by a general radiologist, radiology resident, or attending emergency physician, then the basis on which you are basing your recommendations might shift altogether.

The third consideration is the extent to which the results of your search are applicable to your patient and whether they will change your management or allow you to forego further diagnostic evaluation. Is this true for your patient? van der Wee et al[21] dealt with patients whose pretest risk was considerably higher than your estimation for your patient. You are concerned that in this high-risk population, any diagnostic test may have performed better than in a lower-risk population.[16] LRs from a negative test result that are sufficiently low are very useful to the clinician because they allow the practitioner to consider foregoing further consideration of the clinical entity in question.[11] The LR you derive from the study by van der Wee et al is 0.02, with an upper limit of the 95% confidence interval (CI) of 0.07. A CI is an estimate of the range within which the true value of a measured outcome probably lies. When the desired level of confidence is 95%, the interval in question defines a range of values such that, if the true value lay outside of this range, the value reported would have been observed in fewer than 1 of 20 cases.

The spectrum of patients in the Morgenstern et al[2] article best approximates your patient, although some of their patients had meningismus. The LR for a negative CT scan result calculated from that study is 0.07 (see Table 3). Applying the Fagan nomogram supplied in the article on LRs,[11] and using your initial pretest probability estimate of 15%, you calculate the likelihood of SAH after a negative CT scan result to be between 1% and 2%. This is above the action threshold identified by your patient for deferring an unwanted LP. Because only 15 patients presenting in the first 24 hours had SAH, the upper limit of the 95% CI was 0.44. You are not prepared to do a meta-analysis of the 2 articles, and you consciously decide to slant your calculations to favor patient safety. Therefore, you use the most conservative figure—the upper limit of the 95% CI from the Morgenstern et al study—for your last set of calculations. Using this figure of 0.44 for the LR of a negative CT scan result (and the same pretest probability), the posttest probability falls between 6% and 7%.

There are several issues that affect your calculations and subsequent discussion with the patient. For one, all of these figures are predicated on an accurate interpretation of the CT scan. Because your hospital uses a general radiologist, the results from the studies you have selected may not fully apply to your setting, and a false-negative CT interpretation, if not followed up by an LP, could result in a serious adverse outcome for the patient. Second, you have assumed a 100% specificity of the CT scan; any number less than 100% would further affect the LRs in a direction that would increase the posttest probability of SAH after negative CT scan findings. Third, there are some subtle spectrum issues that would also affect the decisionmaking in the same direction. Because both studies you have used may have included some patients with meningismus, this more acute spectrum of patients with SAH might have improved the performance of CT scanning, although it would simultaneously lower your patient's pretest risk, since she did not have that finding.

You tell the patient that the reading of the CT scan is normal. No blood was detected. You explain to her that even after the CT scan, she still could have as much as a 7% (or 1 in 14) chance of having an SAH and because of the quality of the medical literature that is available, it could possibly be even higher. Based on your analysis of the data and the potential for a bad outcome if SAH is missed, you strongly recommend to the patient that she undergo LP but leave the final decision with her.

## REFERENCES

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# Critically Appraised Topic (CAT): "How good is a negative cranial CT scan result in excluding subarachnoid hemorrhage?"

**Question**
Does a negative result of a noncontrast CT scan performed within 12 hours of onset of headache on a third-generation machine reduce the likelihood of SAH to below 1% in adult patients presenting to an ED with acute, severe headache and a normal neurological examination?

**Reviewed by**
Edlow JA, Wyer PC

**Date**
March 10, 2000

**Expiration date**
March 10, 2002

**Clinical bottom line**
Based on the current best evidence, for patients having a 15% pretest likelihood of SAH, the posttest probability of SAH after a negative CT result for scan done on a third-generation scanner within the first 12 hours is as high as 6% to 7%, possibly higher. Because of the serious consequences of missing an SAH when the patient presents with a normal examination, this falls above the action threshold of most patients and physicians for deferring an LP when the CT scan result is negative.

**Search strategy**
MEDLINE was searched via PubMed for MeSH terms: "subarachnoid hemorrhage," "tomography, x-ray computed," and "spinal puncture." The last term was amplified to include text words: "spinal fluid" and "lumbar puncture." We searched for English language articles published between January 1985 and March 2000. Studies that examined a population of adult patients presenting to an ED with acute onset of severe headache within 12 hours of onset of symptoms and who had a cranial CT scan performed on a third-generation scanner were given priority.

**Citations**
1. Morgenstern LB, Luna-Gonzales H, Huber JC, et al. Worst headache and subarachnoid hemorrhage: prospective, modern computed topography and spinal fluid analysis. *Ann Emerg Med*. 1998;32:297-304.

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**Study characteristics**

**Population**
***Morgenstern et al:*** Adult patients presenting to an ED with the worst headache of their life. Patients were excluded if they had trauma within the prior 3 months, LP within the prior 2 weeks, coagulopathy, thrombocytopenia (<50,000), temperature >38.5°C, head CT evidence of a mass lesion, cerebral edema, or intracerebral hemorrhage, systemic or central nervous system cancer, and focal neurologic signs other than nuchal rigidity and photophobia.
***van der Wee et al:*** Patients admitted to the hospital with acute headache who were oriented, had no focal neurologic deficits on examination, and who had CT scans performed within 12 hours after onset of headache.

**Interventions**
***Morgenstern et al:*** Patients underwent CT scan with a third-generation scanner. Those patients whose scan results were negative, as interpreted by 2 neuroradiologists, then underwent LP. CSF was examined for xanthochromia, RBCs, and D-dimer.
***van der Wee et al:*** Patients underwent CT scan with a third-generation scanner. Patients whose scan results were negative, as interpreted by 2 neurologists and a neuroradiologist, underwent LP that was deferred by at least 12 hours after onset of symptoms. CSF was examined for RBCs and xanthochromia.

**Outcomes**
***Morgenstern et al:*** Of the patients who presented within the first 24 hours, 15 had SAH, 14 diagnosed by CT scan and 1 by LP.
***van der Wee et al:*** Of the 175 patients, 119 had SAH, 117 diagnosed by CT scan and 2 by LP.

**Critical appraisal**
***Morgenstern et al:*** This was the only prospective study of ED patients presenting with worst headache of life and scanned within 24 hours of onset. Patients with negative CT results underwent LP. Of the 170 eligible patients, only 107 (63%) were enrolled. Ten of the enrolled patients refused LP. There were only 15 patients who ruled in for SAH in the group presenting within 24 hours of symptom onset. Patients with bad (but not worst-of-life) headaches were not followed up. Neuroradiologists interpreted the scans. Overall quality: fair to good.
***van der Wee et al:*** This study involved admitted patients with severe acute headache scanned within 12 hours after onset of their symptoms; 119 of the 175 patients studied had SAH, a proportion far higher than the pretest risk for most series of outpatients. The proportion with meningismus is not specified, and admission criteria were not specified. Two neurologists and a neuroradiologist jointly interpreted the scans. Overall quality: fair.

**Results**
***Morgenstern et al:*** Of the 170 patients presenting within 24 hours from onset of headache, 15 had SAH. CT diagnosed 14; LP diagnosed 1. Using blood on the CT scan as the criterion for a positive scan, the LR of a negative CT scan result in excluding SAH was 0.07 (upper limit of the 95% CI 0.44).
***van der Wee et al:*** Of the 175 patients who had CT scans performed within 12 hours from onset of headache, 119 had SAH. CT diagnosed 117; LP diagnosed 2. Blood on CT scan was the criterion for a positive scan; the likelihood ratio of a negative CT scan result in excluding SAH was 0.02 (upper limit of the 95% CI 0.07).