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Determination of a Testing Threshold for Lumbar Puncture in the Diagnosis of Subarachnoid Hemorrhage after a Negative Head CT: A Decision Analysis

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Author Contributions:

RAT and DHN conceived, designed, and supervised the study. HSG and EGM provided expert review of the structure of the decision analysis. HPM, JSF, and DHN undertook literature review and acquisition of the data. RAT analyzed the data. RAT drafted the manuscript, and all authors contributed substantially to its revision. RAT takes responsibility for the paper as a whole.

Abstract:

Objective

To determine the testing threshold for lumbar puncture (LP) in the evaluation of aneurysmal subarachnoid hemorrhage (SAH) after a negative head CT. As a secondary aim we sought to identify clinical variables that have the greatest impact on this threshold.

Methods

A decision analytic model was developed to estimate the testing threshold for patients with normal neurologic findings, being evaluated for SAH, after a negative CT of the head. The testing threshold was calculated as the pretest probability of disease where the two strategies (LP or no LP) are balanced in terms of quality adjusted life years (QALYs). Two-way and probabilistic sensitivity analyses (PSA) were performed.

Results

For the base case scenario the testing threshold for performing an LP after negative head CT was 4.3%. Results for the two-way sensitivity analyses demonstrated that the test threshold ranged from 1.9%-15.6%, dominated by the uncertainty in the probability of death from initial missed SAH. In the PSA the mean testing threshold was 4.3% (95%CI, 1.4-9.3). Other significant variables in the model included: probability of aneurysmal versus non-aneurysmal SAH after negative head CT, probability of long-term morbidity from initial missed SAH, and probability of renal failure from contrast induced nephropathy.

Conclusions

Our decision analysis results suggest a testing threshold for LP after negative CT to be approximately 4.3%, with a range of 1.4% to 9.3% on robust PSA. In light of these data, and considering the low probability of aneurysmal SAH after a negative CT, classical teaching and current guidelines addressing testing for subarachnoid hemorrhage should be revisited.

Introduction

Background

Aneurysmal sub-arachnoid hemorrhage (SAH) is a common concern in the evaluation of neurologically normal patients with headache, but an uncommon occurrence. Headaches account for approximately 2% of annual emergency department (ED) visits, though SAH accounts for less than 1% of these.[1] Misdiagnosis and morbidity rates associated with SAH are high,[2] and current clinical practice guidelines[3,4] recommend lumbar puncture after a negative non-contrast computed tomography (CT) despite a very low probability of disease.[5]

Importance

Lumbar puncture, however, is not without risks including meningitis, neurologic injury, and patient harm from further pursuit of false positive results.[6-8] Attempts to balance these complex processes has made the decision of whether to perform lumbar puncture following CT a decision point with both high clinician variability[2,9] and with the potential for important impact on patient outcomes.[10]

Decision analysis is a mathematical modeling technique well suited to analyzing complex medical problems with multiple components and determining optimal decision strategies under varying conditions.[11] Among headache patients considered for lumbar puncture, decision analysis allows for the determination of the comparative impact, in quality adjusted life years (QALYs), of performing versus not performing lumbar puncture at different pretest probabilities of disease. The pretest probability of disease where the two strategies are balanced in terms of QALYs is known as

the testing threshold, and represents the acceptable miss rate (i.e. if testing was performed at pretest probabilities lower than the threshold the risks of harm to the patient from further testing would outweigh the risk of benefit).[12]

Goals of This Investigation

The primary aim of our study was to determine the testing threshold for lumbar puncture in the evaluation of SAH after a negative non-contrast head CT. As a secondary aim we planned to identify clinical variables that have the greatest impact on this threshold.

Materials and Methods

Study Design

This study was a decision analysis developed according to published guidelines[13] to estimate the testing threshold for performing lumbar puncture after a negative non-contrast CT in the evaluation of a patient for SAH. As a decision analysis, the study was only dependent upon data from literature review or expert opinion and was exempt from review by our institutional review board.

Setting

The hypothetical base case for our decision analytic model is a 45-year-old patient presenting to the emergency department with a headache and normal neurologic findings, being evaluated for SAH, after a negative non-contrast computed tomography of the head. Forty-five years represents roughly the mean age of neurologically normal patients enrolled in prospective studies designed to capture patients with SAH and those in whom SAH is an important diagnostic consideration.[9,10,14] In our clinical scenario after negative imaging the provider is confronted with two potential diagnostic strategies: perform lumbar puncture with further testing guided by the results, or omit lumbar puncture and presumably discharge the patient. Subsequent diagnostic and management strategies were chosen to reflect standard practice and accepted guidelines for the evaluation and management of SAH.[3,15,16]

Model Structure

To model the clinical scenario and diagnostic pathways described above, we constructed a decision tree (Figure 1) using decision analysis software (TreeAge Pro 2013, TreeAge Software, Williamstown, MA). The primary node of the decision tree represents the decision to perform or not perform lumbar puncture. If the provider chooses to perform lumbar puncture and the findings are positive for xanthochromia or blood then computed tomographic angiography is performed. If the lumbar puncture is negative, the patient is not further evaluated. For those patients with a positive lumbar puncture, if angiography is positive for a cerebrovascular aneurysm, then the patient potentially undergoes surgical or endovascular aneurysmal repair. Those patients with a positive lumbar and with a negative angiography are not further evaluated for SAH and are treated with standard care. Branch probabilities for the nodes of these diagnostic tests represent the sensitivity and specificity of the test transformed through Bayesian revision into decision probabilities (i.e. the false positive, false negative, true positive, and true negative probabilities). Additional branch points within the model represent the probability of certain events occurring (chance nodes) and the transition between several disease states (e.g. cancer) with continuing risk over time (Markov nodes).

Terminal nodes within the model represent final outcomes and were assigned values or "payoffs" based on QALYs.[17] For each year within the model, a particular outcome is associated with a utility value that estimates the quality of life for that individual in a particular disease state with death equal to zero and perfect health equal to one. To account for the comparative value of future life-years we assumed a standard discount rate of 3%.[18] For health states in which more than one disease state was possible (e.g. a patient having cancer and long-term morbidity from SAH) the utility values were multiplied together to obtain the composite utility value.[19]

Several assumptions were made in the construction of the model to decrease complexity. First, in the first year only the outcome of mortality was considered. This restriction enabled the exclusion of multiple potential branch points for short-term (<1 year) morbidity that were unlikely to have overall model effects including: effects from contrast induced nephropathy (CIN) without the need for renal replacement therapy (RRT); and short-term morbidity from RRT, lumbar puncture, anaphylaxis, and SAH. Second, we assumed that death directly attributable to meningitis from

lumbar puncture, anaphylaxis, or dialysis-dependent renal failure only occurred within the first year. Third, gender differences in outcomes were not explicitly built into the model, however gender was factored into the upper range of life expectancy. Last, we assumed the patient did not have comorbidities that would differentially affect outcomes.

Model Inputs and Data Collection

Data for the model inputs (Tables 1 & 2) were obtained from a methodical literature search and review, with ancestral search of available evidence for each topic. Using the Integrated Search Interface Web of Knowledge, Google Scholar, and PubMed in 2015, we searched for articles by combining terms *subarachnoid hemorrhage*, *lumbar puncture*, *CT or computed tomography*, *contrast-induced nephropathy or acute renal failure*, *radiation*, and *cerebral aneurysm* in logic based queries. Two investigators (HM and JF) blinded to study hypothesis reviewed articles or abstracts to determine relevance, extract data using a standardized data form, and grade methodologic quality according to standardized criteria, with disputes resolved by a third reviewer (DN). Credible intervals were constructed using the range of values suggested in the literature, with embedded confidence intervals where appropriate (typically from systematic reviews with high quality, low heterogeneity meta-analysis).

In modeling the clinical evaluation and treatment of SAH, there are a number of pathophysiologic factors and clinical complications that were considered as inputs for the model. Not all SAHs are the result of aneurysmal bleeding, particularly after a negative head CT. This is supported by data from the largest prospective cohort study examining emergency department headache evaluation for SAH, in which approximately 20% of patients diagnosed with SAH after negative computed tomography evaluation were found to have evidence of an underlying aneurysm.[9,20] There is an estimated 0.4-7% prevalence of asymptomatic aneurysms in the general population.[21] For false positive lumbar punctures (i.e. false positive SAH), aneurysms found on CTA will be presumed to be causative and will typically lead to therapeutic procedures (e.g. surgical clipping or endovascular coiling) with the potential for complications including death.[22,23] There are also multiple complications that may arise from lumbar puncture. In our model post lumbar puncture headache and the discomfort of the procedure itself were not considered, as we felt these represented short-term morbidity that would be difficult to reliably model or convert into QALYs.[24] However, we did consider the very small risks of meningitis and paraparesis from lumbar puncture as these contribute to mortality and long-term morbidity.[6-8] Given the limited amount of information on LP adverse outcomes, within our sensitivity analyses we set the lower bounds of mortality and morbidity rates to 0%. In addition, the model includes complications of contrast administered for CTA (e.g., death from anaphylaxis and renal failure, and long-term dialysis dependence).[25-29] Furthermore, the transition of the patient through various states of cancer(i.e. no cancer, cancer, and death) and from the state of having long-term morbidity from SAH to death form SAH were incorporated into Markov nodes.

Data Analysis

To determine a testing threshold for lumbar puncture for our base case a one-way sensitivity analysis was performed to examine the impact that pretest probability of disease has on the model while other variable inputs were held constant. The testing threshold is the pretest probability at which both decisions are equally effective (i.e. produce the same number of QALYs).

Two-way sensitivity analyses were performed to evaluate the influence of model variables on the testing threshold and to account for variable uncertainty in the model. When available, a range of values for each variable was obtained from 95% confidence intervals and credible intervals constructed from literature searches as note above. When these were unavailable a range was derived through assumption and group consensus. Results of the two-way sensitivity analyses are expressed in a tornado diagram.

A limitation of two-way sensitivity analysis is that it is only two-way (i.e. all other variables except two are held constant) and thus unable to examine uncertainty within the model that results from the interaction of more than two variables. To better determine the uncertainty and range of values for the testing threshold, we further analyzed the model through probabilistic sensitivity analysis (PSA) and Monte Carlo Simulation.[30] We assumed beta probability distributions for the model variables with distribution parameters determined by data available from literature review or, when not available, assumption and group consensus.[31] Monte Carlo simulation was performed with

500,000 iterations in which each iteration selected random values from the probability distributions of each variable. A testing threshold with 95% confidence intervals (CI) was determined by analyzing the values of the pretest probability of disease for iterations in which the outcomes for the two decision strategies were equal.

Results

For the base case scenario (45 year-old presenting to the ED with a headache, normal neurologic status, and negative head computed tomography) based on one-way sensitivity analysis the testing threshold for lumbar puncture was 4.3%. Adjustments for gender based life expectancy had no effect.

Results of the two-way sensitivity analyses for each variable in the model are demonstrated in Figure 2. In examining all variables in the two-way sensitivity analysis, the range of the test threshold, was 1.9%-15.6%, dominated by the uncertainty in the probability of death from initial missed SAH. Other significant drivers of model variation included: probability of aneurysmal versus non-aneurysmal SAH after negative head CT, probability of long-term morbidity from initial missed SAH, and probability of renal failure requiring RRT from CIN. In the probabilistic sensitivity analysis the mean testing threshold was 4.3% (95%CI, 1.4-9.3).

Discussion

The approach to diagnostic testing for specific conditions can be examined and potentially improved by consideration of a threshold for testing at which potential harms and benefits of testing are equal. Within the context of shared decision making, this information can be used to guide both physicians and patients. In the setting of potentially deadly conditions, however, the utility of this threshold is often overshadowed by barriers including defensive practice due to medico legal or professional concerns, patient expectation, poor communication, and a focus on diagnostic certainty. We are unaware of prior published literature estimating a testing threshold for lumbar puncture in the setting of potential SAH after a negative CT.

Our decision analysis calculations suggest that a reasonable test threshold for performance of lumbar puncture for the detection of subarachnoid hemorrhage in neurologically normal patients with headache and a negative non-contrast head CT is approximately 4.3%, with a range of 1.4% to 9.3% in a robust PSA analysis. These findings contrast with common practice and classical teaching both of which tend to focus on the potential benefits of diagnosis without explicit consideration of harms arising from testing.[32]

The testing threshold after negative imaging in our analysis was raised by a number of factors. First, in relevant large studies subjects diagnosed with SAH by lumbar puncture appear to have mostly non-aneurysmal SAH or false positive lumbar punctures.[9,14] Because non-aneurysmal atraumatic SAH is associated with nearly universal complete recovery without therapy, detection in such cases yields no improvement in QALYs. Second, data suggest that delays in diagnosis, while undesirable and potentially dangerous, lead to morbidity or mortality in a minority (roughly 10%) of missed aneurysmal subarachnoid hemorrhage.[10,33-35] Third, lumbar puncture includes small but real risks of infection and injury.[6-8] Finally, patients with positive lumbar puncture findings typically undergo angiography, incurring risks of anaphylaxis, contrast-induced nephropathy, and additional radiation exposure. Moreover, incidental aneurysms found during angiography, present in up to 7% of screening populations[21] will commonly be interpreted as culprit lesions and undergo neurosurgical procedures[22] that include considerable harm rates.[36]

It is not surprising that the variable with the largest impact on the uncertainty of the model was the probability of death from initial missed aneurysmal SAH, as it is the primary serious outcome from not performing LP and has a wide 95%CI reported in the literature. Most other important variables were also associated with SAH outcomes. It is also of note that excluding the direct negative effects of LP (morbidity and mortality associated with infection and neurology damage) fails to lower the testing threshold below a level that would favor performing an LP after negative CT in most patients.

Using testing threshold estimates in clinical practice depends upon knowing the probability of SAH after a negative non-contrast head CT. Fortunately, an increasingly high quality database of prospective studies has begun to fill gaps that have long hampered attempts to examine this issue based on outcomes data.[2,9,10,14] These investigations, when combined with our analysis, strongly suggest that in most patients with acute headache lumbar puncture after negative CT with newer generation scanners, especially when performed under 6 hours of symptom onset, is a more harmful than helpful strategy. This results are also supported by a recent cost-effectiveness study that demonstrated when the CT sensitivity is >99% (i.e. CT on newer generation scanner performed less 6 hours from onset of symptoms) no further testing is warranted.[58] For carefully selected patients (those with a high probability of disease (>20%) and who present late >2 days the likelihood of SAH may exceed testing thresholds in the lowest range of our intervals, suggesting that lumbar puncture may be a beneficial approach for such patients presuming the most conservative estimates for all input variables (Figure 3). Because of the declining performance of CT for SAH over time and the complicated aspect of determining a pre-CT probability of disease, we believe decision aids such as figure 3 coupled with clinical decision rules that estimate pre-CT probabilities of disease will be helpful in making shared decisions with patients under uncertainty.

Limitations

The strength of a decision analysis is dependent upon the validity of variable input and the structural assumptions of the model. In our model there are limitations based on the quality and validity of the available literature addressing each input, and the inferences that can be reasonably made from observational data. Ideally, there would be randomized trial data to inform outcome predictions based on LP and non-LP approaches following negative CT in such patients. To mitigate these uncertainties we used best available data from a rigorous literature search and review, and we employ credible intervals that offer the existing range of published data (rather than 95% confidence intervals) as a means of broadening the potential outputs from our model. In this regard we find it reassuring that varying the statistically most important inputs has a limited impact on decision-making.

As noted above, we made several assumptions regarding the structure of the model to decrease complexity. We chose not to include the short-term effects of lumbar puncture, anaphylaxis, and SAH (e.g. headache, short-term cognitive deficits) as they are extremely unlikely to contribute to any significant change in the model when compared to more serious long-term effects and death. In addition, we chose not to model cost or other diagnostic testing strategies (e.g. CT/CTA then possible LP, or MRI). Cost was not considered as there is no clear accepted standard about the cost per QALY individuals or society would be willing to pay.[37] The strategy of CT/CTA as an initial step is fraught with the consequences of identifying a significant portion of patients with benign headache and incidental aneurysm and previous analysis has shown this strategy to be less effective than CT/LP.[38] A strategy incorporating MRI was not examined because of its reduced availability in acute care settings.[39]

Conclusion

In conclusion, our data suggest an explicit threshold approach to lumbar puncture testing for neurologically normal, CT-negative acute headache patients. Our decision analysis calculations suggest this threshold to be approximately 4.3%, with a range of 1.4% to 9.3%. In light of these data, and considering the low probability of aneurysmal SAH after a negative CT, classical teaching and current guidelines addressing testing for subarachnoid hemorrhage should be revisited.

Table 1. List of input variables for Decision Analytic Model

Variable	Value, %	Range for Sensitivity Analysis, %	Category in Model	Source
LP sensitivity for SAH	100	94-100	Bayesian	[14,40]
LP specificity for SAH	67	63-71	Bayesian	[14,40]
CTA sensitivity for Aneurysm	98	97-99	Bayesian	[22,41]
CTA specificity for Aneurysm	100	97-100	Bayesian	[22,41]
Probability of LP long-term morbidity	0.1	0-0.2	Probability	[7]
Probability of Death from LP	0.02	0-0.1	Probability	[8,24,42]
Probability of ARF requiring RRT secondary to CIN	.1	0-1	Probability	[25,28]
Probability of death from ARF requiring RRT secondary to CIN	35.4	20-100	Probability	[26,27]
Probability of Death from Surgery for asymptomatic aneurysm	2.5	0.8-3.2	Probability	[36,43]
Probability of Long-Term Morbidity from Surgery for asymptomatic aneurysm	9.2	8.1-10.4	Probability	[36,43]
Probability of death from Anaphylaxis	0.0021	0.0001-0.027	Probability	[29,44]
Probability of aneurysmal vs. non-aneurysmal SAH (after negative CT) ¥	20	10-50	Probability	[20]
Probability of incidental aneurysm	2	0.4-6	Probability	[21,45,46]
Probability of death SAH non-aneurysmal	2.6	0.7-9.0	Probability	[47]
Probability of long-term morbidity non-aneurysmal SAH	0	0-4.8	Probability	[47]
Probability of Death from SAH (treated/initial correct diagnosis)	5	2-9	Probability	[10,48,49]
Probability of long-term morbidity (treated/initial correct diagnosis)	31	24-38	Probability	[10,48,49]
Probability of Death from initial missed aneurysmal SAH	19	9-35	Probability	[10,48,49]
Probability of long-term morbidity from initial missed aneurysmal SAH	31	17-49	Probability	[10,48,49]
Annualized long-term mortality rate for SAH morbidity patients*	5	0-10	Markov	[50,51]
Annual cancer rate from CT (head)	.00035	0-.001	Markov	[52-54]
Annual mortality from cancer (head)	13%	5-50%	Markov	[55,56]
Annual remission (without symptoms) from cancer	5%	1-10%	Markov	[56]

Patient Age (years)	45	18-70	Markov	[9]

* Calculated from the lifetime attributable risk (LAR) of cancer incidence using the linear no-threshold model from the BEIR VII report[13] and division by the LAR of cancer incidence by the number of cycles in the model to arrive at a per year risk of cancer.

¥ Conservative estimate based on available data using positive LP definition of 500 rbcs/hpf

Multiple data sources were combined where possible as a weighted averages based on study sample size.[57]

Terms: LP(lumbar puncture), SAH(subarachnoid hemorrhage), ARF (acute renal failure), RRT (renal replacement therapy), CIN (contrast-induced nephropathy)

Table 2. List of Utility Values for Decision Analytic Model

Variable	Value, %	Range for Sensitivity Analysis, %	Category in Model	Source
Utility for ARF requiring RRT	0.84	0.7-0.9	Utility	[17]
Utility of LP morbidity (paraparesis)	0.7	0.6-0.9	Utility	[17]
Utility of Long Term morbidity from SAH	0.76	0.6-0.9	Utility	[17]
Utility of combined cancer and ARF requiring RRT*	0.67	0.49-0.81	Utility	Calculated
Utility of combined cancer and LP morbidity*	0.56	0.49-0.81	Utility	Calculated
Utility of combined cancer and SAH morbidity*	0.56	0.42-0.81	Utility	Calculated
Utility of combined cancer, ARF RRT, LP morbidity*	0.47	0.29-0.73	Utility	Calculated
Utility of combined cancer, ARF RRT, SAH Morbidity*	0.51	0.29-0.73	Utility	Calculated
Utility of combined cancer, ARF RRT, LP and SAH Morbidity*	0.35	0.18-0.66	Utility	Calculated
Utility of combined cancer, LP and SAH morbidity*	0.43	0.25-0.73	Utility	Calculated
Utility of combined ARF RRT, LP and SAH*	0.45	0.25-0.73	Utility	Calculated
Utility of combined LP and SAH morbidity*	0.53	0.36-0.81	Utility	Calculated
Discount rate	3%		Markov	[18]

* Combined utility values formed from multiplying individual values[19]

Captions for Figures

Figure 1A&B
Representative components of the decision tree on whether to perform lumbar puncture after a negative non-contrast head CT. Figure 1A represents the base of tree with initial decision node (square) and subsequent downstream chance, or probability nodes (circles), and terminal nodes (triangles). Breaks in lines represent further aspects of the decision tree, part of which is demonstrated in figure 1B with Markov nodes (circles with "M").

Figure 2

Tornado diagram of two-way sensitivity analyses of variables in model and their effect on the testing threshold.

Figure 3

Conceptual model showing interaction of pre-CT probability of disease, time from onset of headache, and sensitivity of CT for subarachnoid hemorrhage. Assumed linear decrease in CT sensitivity of 5% every 12 hours, and constant specificity of 99%. Lower 95% bound (1.4) and mean value (4.3) of testing threshold are displayed. The intersection of the threshold and probability lines represent time points before which, according to our analysis, performing an LP causes more harm than good for a given pre-test probability of disease.

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