Cost-Effectiveness of Angiographic Imaging in Isolated Perimesencephalic Subarachnoid Hemorrhage

Vivek B. Kalra, MD; Xiao Wu, BS; Howard P. Forman, MD, MBA; Ajay Malhotra, MD

Background and Purpose—The purpose of this study is to perform a comprehensive cost-effectiveness analysis of all possible permutations of computed tomographic angiography (CTA) and digital subtraction angiography (DSA) imaging strategies for both initial diagnosis and follow-up imaging in patients with perimesencephalic subarachnoid hemorrhage on noncontrast CT.

Methods—Each possible imaging strategy was evaluated in a decision tree created with TreeAge Pro Suite 2014, with parameters derived from a meta-analysis of 40 studies and literature values. Base case and sensitivity analyses were performed to assess the cost-effectiveness of each strategy. A Monte Carlo simulation was conducted with distributional variables to evaluate the robustness of the optimal strategy.

Results—The base case scenario showed performing initial CTA with no follow-up angiographic studies in patients with perimesencephalic subarachnoid hemorrhage to be the most cost-effective strategy ($5422/quality adjusted life year). Using a willingness-to-pay threshold of $50000/quality adjusted life year, the most cost-effective strategy based on net monetary benefit is CTA with no follow-up when the sensitivity of initial CTA is >97.9%, and CTA with CTA follow-up otherwise. The Monte Carlo simulation reported CTA with no follow-up to be the optimal strategy at willingness-to-pay of $50000 in 99.99% of the iterations. Digital subtraction angiography, whether at initial diagnosis or as part of follow-up imaging, is never the optimal strategy in our model.

Conclusions—CTA without follow-up imaging is the optimal strategy for evaluation of patients with perimesencephalic subarachnoid hemorrhage when modern CT scanners and a strict definition of perimesencephalic subarachnoid hemorrhage are used. Digital subtraction angiography and follow-up imaging are not optimal as they carry complications and associated costs. (Stroke. 2014;45:00-00.)

Key Words: angiography • digital subtraction

Isolated perimesencephalic subarachnoid hemorrhage (pSAH) is a distinct imaging and clinical entity that constitutes 5% of patients with subarachnoid hemorrhage (SAH). pSAH has specific imaging criteria, as defined by van Gijn et al.1 Because 10% of pSAH pattern bleeds are caused by posterior circulation aneurysms, and aneurysmal bleeds have high morbidity and mortality when left untreated, an initial angiographic study is warranted to exclude aneurysm. There has been extensive controversy regarding what this initial angiographic study should be and whether follow-up is needed in these patients after an initial negative angiographic study. Computed tomographic angiography (CTA) and digital subtraction angiography (DSA) have both been used for initial angiographic evaluation. The type (CTA versus DSA) and number of follow-up angiographic studies performed have cost implications amenable to a cost-effectiveness study.

The controversy regarding what follow-up is needed in patients with pSAH after negative CTA hinges on the sensitivity of CTA to detect aneurysms, responsible for ≤10% of pSAH cases. Published CTA sensitivities for aneurysm detection vary from 75% to 99%, depending on CT technology, and result in markedly different conclusions regarding CTA’s negative predictive value. Published CTA and DSA comparative studies have not fully accounted for change in technology over time and the different complication rates between noninvasive and invasive modalities. DSA, conventionally considered as the reference standard test for aneurysm detection, is an invasive procedure that can have complications at the arterial puncture site and from intravascular emboli resulting in transient ischemic attack, stroke, and even death. Both DSA and CTA share similar risks regarding radiation, contrast-induced allergic-like reaction, and contrast-induced nephropathy.

The purpose of this study is to perform a comprehensive cost-effectiveness analysis of all possible permutations of CTA and DSA imaging strategies for both initial diagnosis and follow-up imaging, without the option of observation (with no
angiographic studies). The parameters of the analysis model were derived from a meta-analysis of 40 studies and published literature values and assigned plausible distributions to allow for variation in the Monte Carlo simulation (probabilistic sampling).

Table. Expected Costs and Utilities in Base Case Scenario

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Expected Cost (Lower Is Better)</th>
<th>Expected Utility (QALY; Higher Is Better)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTA+no follow-up</td>
<td>$4221</td>
<td>0.778445479</td>
</tr>
<tr>
<td>CTA+CTA</td>
<td>$4934</td>
<td>0.778126165</td>
</tr>
<tr>
<td>DSA+no follow-up</td>
<td>$11750</td>
<td>0.775816218</td>
</tr>
<tr>
<td>Both+no follow-up</td>
<td>$12665</td>
<td>0.773445186</td>
</tr>
<tr>
<td>CTA+DSA</td>
<td>$12665</td>
<td>0.773445186</td>
</tr>
<tr>
<td>DSA+CTA</td>
<td>$12726</td>
<td>0.773421837</td>
</tr>
<tr>
<td>CTA+both</td>
<td>$13581</td>
<td>0.771074154</td>
</tr>
<tr>
<td>Both+CTA</td>
<td>$13648</td>
<td>0.771051277</td>
</tr>
<tr>
<td>DSA+DSA</td>
<td>$20172</td>
<td>0.772836622</td>
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<tr>
<td>Both+DSA</td>
<td>$21110</td>
<td>0.770550456</td>
</tr>
<tr>
<td>DSA+both</td>
<td>$21114</td>
<td>0.770526558</td>
</tr>
<tr>
<td>Both+both</td>
<td>$22061</td>
<td>0.768214494</td>
</tr>
</tbody>
</table>

CTA indicates computed tomographic angiography; DSA, digital subtraction angiography; and QALY, quality adjusted life year.

Methods

Model Design

This cost-effectiveness analysis is conducted from a societal perspective. A decision tree was built with TreeAge Pro Suite 2014 (TreeAge Software, Inc, Williamstown, MA) with starting point of an initial noncontrast CT scan demonstrating bleeding pattern meeting strict criteria of pSAH in a nontraumatic setting. The 12 potential options at the initial decision node are listed in the Table. The strategy of not performing any angiographic imaging was not considered because this is not clinically acceptable, given the 10% prevalence of posterior circulation aneurysms in patients with pSAH.2

At each strategy arm, there was a probability of detecting posterior circulation aneurysms, or returning negative result at initial diagnostic imaging. The arm labeled positive initial comprised true and false positives. The alternative arm of the node was labeled negative initial, representing our target population. From the negative initial node, both true and false negatives were possible. From strategies with no follow-up imaging, false negative results were regarded as untreated aneurysms. For strategies with follow-up imaging, true negative node may have a true negative CTA or DSA follow-up, or a false positive CTA result. A false negative node may have a true positive or false negative on follow-up imaging. Detected aneurysms were regarded as treated. Complications resulting from both initial and follow-up imaging in true negative cases were discussed. Missed aneurysms were regarded as untreated, with a significantly higher cost and lower expected utility. Terminal nodes were assigned to each arm, with specified cost and effectiveness. The complete model of this cost-effectiveness is provided in Figure 1 and Figure I in the online-only Data Supplement.

Figure 1. Decision tree of selected nodes. CTA indicates computed tomographic angiography; DSA, digital subtraction angiography; and FU, follow up.
Model Parameters

Diagnostic Test Parameters
Initial CTA was assigned a sensitivity of 99.2% and specificity of 99.2%, based on a meta-analysis of 16 and 64 row scanners with >493 patients. Follow-up CTA was assigned a lower sensitivity (84%–94%) and specificity (90%–100%), as the aneurysms missed on an initial study are likely to be <3 to 4 mm and prone to reader misinterpretation on follow-ups. DSA, being the reference standard, was assigned 100% for both sensitivity and specificity.

Clinical Probabilities
Each probability in this model was based on published literature values. The rate of detecting an initially occult aneurysm by follow-up DSA in patients undergoing both DSA and CTA as initial diagnosis was given 0.12%, based on a meta-analysis of 40 studies and from published sensitivities and specificities of CTA for the remaining strategies. The probability of reaching each terminal node was calculated along the path from the starting decision node, with Bayesian updating when necessary. If aneurysm was preceded by a false negative node, the outcome probabilities were constructed to reflect the poor natural history of an untreated ruptured aneurysm. If aneurysms were detected from the posterior circulation aneurysm node, probabilities were constructed to reflect the outcome of patients with treated ruptured aneurysms. If aneurysm node was reached from other paths, it then corresponded to an initially occult aneurysm.

Probability of complications for CTA and DSA was assigned published literature values. Complications shared by CTA and DSA include radiation, contrast-induced allergic-like reaction, and contrast-induced nephropathy. DSA can have variable dosages for contrast and radiation, frequently greater than those used in CTA, but were assigned as the same for the purposes of this analysis. Complications specific to CTA include contrast infiltrations, which is uncommon and reported in 0.7% cases. Most cases are mild or moderate and only require inexpensive treatments such as ice packs, splint, silver sulfadiazine, or antibiotics. Only one in 61,916 adult patients (0.0016%) were reported to have a severe compartment syndrome, which required surgery. Contrast infiltration was thus not included as a node in our decision model, as it would only have minimal impact on costs and utilities. Radiation-associated stochastic risks were not included in the model.

Costs
Total cost at each terminal node was derived by totaling all the costs along its path, which were determined using 2013 US regional Medicare reimbursement values when possible. Patients' out-of-pocket expenses were not included because this study was conducted from a societal perspective. DSA was assumed to consist of a 6-vessel angiogram (bilateral internal carotid arteries, bilateral external carotid arteries, and bilateral vertebral arteries) when computing costs. Costs incurred from complications were derived from the literature, adjusted for inflation and foreign currency converted to time-adjusted US dollar values in 2014, then multiplied by the purchasing power parity factor. To minimize bias and subjectivity, each cost was assigned to have a normal distribution with a SD of 10% in the Monte Carlo simulation.

Utilities
Each terminal node was assigned a utility value according to the modified Rankin scale score and a value was based on quality adjusted life year. A modified Rankin scale of 0 to 2 corresponded to a good outcome, modified Rankin scale of 3 to 5 corresponded to a poor outcome, and modified Rankin scale of 6 corresponded to death. The exact value for each outcome was obtained from Samsa et al with a variation range for Monte Carlo simulation. A detailed list of all parameters, their values, distributions (when applicable), and references is presented in Table I in the online-only Data Supplement.

Statistical Analyses
Analyses were performed using TreeAge Pro Suite 2014 (TreeAge, Inc, Williamstown, MA). The cost-effectiveness of each initial and follow-up strategy was evaluated at the corresponding decision node, and Monte Carlo simulation was performed over the range of each distributional variable with 10,000 iterations.

Results

Base Case Scenario
In the base case scenario, the expected cost and utility of each strategy were used to evaluate the cost-effectiveness of each strategy. CTA+no follow-up was shown to be the most cost-effective strategy at a willingness-to-pay (WTP) threshold of $50,000/ quality adjusted life year (Figure 2). The respective cost and expected utility of each strategy are presented in the Table with strategies ranked in ascending cost.

The cost-effectiveness analysis based on incremental cost-effectiveness ratio demonstrated that CTA+no follow-up strictly dominates all other strategies. CTA+CTA is a close second strategy.

One-Way Sensitivity Analysis
One-way sensitivity analysis was performed by varying the sensitivity of the initial CTA. Using a WTP threshold of $50,000/quality adjusted life year, the most cost-effective strategy based on net monetary benefit is CTA+no follow-up when the sensitivity of initial CTA is >97.8%, and CTA+CTA otherwise (Figure 3).

Monte Carlo Simulation
A Monte Carlo simulation was performed with 10,000-iteration probabilistic sampling. Results demonstrate that CTA+no follow-up is the most cost-effective strategy in 100% of the cases at the $50,000/quality adjusted life year WTP threshold. CTA+no follow-up is the optimal strategy in 99.99% of iterations even at a $1 million WTP strategy when using initial CTA sensitivity of 99.2%.

A scatter plot of CTA+CTA against CTA+no follow-up is presented in Figure 4, with CTA+CTA being less cost-effective (above the WTP=50,000 line) in most of the iterations.

Discussion
Controversy continues regarding type of initial and amount of follow-up imaging in pSAH. Ten percentage of pSAH is secondary to ruptured posterior circulation aneurysm, and the need for follow-up imaging is dependent primarily on the sensitivity of the initial angiographic study. Technological advances have markedly improved the sensitivity of CTA in the past decade to detect small aneurysms, decreasing the need for additional angiographic imaging. In addition, more accurate data regarding the risks of invasive and noninvasive iodinated-contrast angiographic imaging have been published based on larger patient populations. An updated comprehensive cost-effectiveness study was needed to account for these technological advances and improved statistics regarding angiographic imaging complications. These improvements were not fully accounted for in prior decision analysis models, as some based their parameters on
older studies or those with smaller patient populations, in a similar cost-effectiveness analysis by Sailer et al., the sensitivity and specificity of CTA were given as $\beta$ distributions with means of 91.5% and 94.4%, respectively. Jethwa et al. assigned CTA’s negative predictive value a normal distribution with a mean of 95.7% and a SD of 0.8%, equivalent to a 72.3% maximum sensitivity of CTA given the 10% prevalence of posterior circulation aneurysms in pSAH. Modern 16 and 64 row scanners allow for a resolution on a submillimeter scale (0.5–0.7 mm), allowing for accurate detection of small aneurysms. Sixty-four row scanners were found to have an overall 99.2% sensitivity and specificity per patient, and 94% sensitivity for aneurysms <4 mm in a meta-analysis of 8 studies, pooling >493 patients. These sensitivities and specificities are far higher than the assigned values in the abovementioned studies. We assigned these values to the initial CTA because 16 and 64 slice scanners are the most commonly used CT scanners in the United States in 2012. However, there is no consensus on the sensitivity and specificity of CTA as a follow-up study on patients with negative initial CTA results. Some papers assigned 100% specificity to second CTA, whereas others cited a much lower value. Given the wide range of values in literature, we assigned a lower range (84%–94%) for second CTA sensitivity with a uniform distribution in patients with negative initial studies, as aneurysms missed on the initial studies are likely <4 mm.

DSA was assigned a 100% specificity and sensitivity in both our model and past studies because it is considered to be the reference standard. However, DSA is an imperfect gold standard because it is both operator and interpretation dependent. Monoplane DSA has been described as having a false negative rate of 7.1% compared with second examination. Biplane DSA missed >1 out 5 aneurysms measuring <3 mm using rotational angiography as the reference standard. DSA using 3-dimensional rotational angiography was found to have a sensitivity of 99.3% when surgical findings were used as the reference standard.

Complication rates from CTA and DSA also have a significant impact on determining cost-effectiveness of imaging strategies. Jethwa et al. underestimated the complication rates of hematoma, nephropathy, and stroke, assigning them as $\beta$ distributions with means of 0.4%, 0.5%, and 0.2%, respectively. Their values were primarily based on 2 3000-patient studies. In addition, they did not consider iodinated-contrast allergic-like reactions. Sailer et al. did not differentiate among the complications of DSA giving them an overall probability of 0.2% and did not account for any complication of CTA, leading them to conclude that DSA+CTA was the optimal imaging strategy. Ward et al. used an 11.6% incidence of contrast-induced nephropathy, grossly overestimating the complication rate of CTA. On our literature search, a study with 19826 patients reported the rate of hematoma as 4.2%, nephropathy as 0.02%, transient ischemic attack as 2.45%, stroke as 0.14%, and death as 0.05%. Another study, also with over 19000 patients, reported the rates of mild and severe allergic-like reactions as 0.56% and 0.04%, respectively, totaling to a CTA.
complication rate of <0.7% and a DSA complication rate of ≈7%. Some decision models, such as the one by Ward et al19a considered tumor as a possible complication from radiation.

As per the International Organization for Medical Physics, risk of radiation-induced cancer and cancer death should not be estimated for doses ≤100 mSv, markedly greater than the 3

Figure 3. One-way sensitivity analysis. The net monetary benefit is defined as effectiveness×willingness-to-pay–cost, and a higher monetary benefit is more desirable. CTA indicates computed tomographic angiography; DSA, digital subtraction angiography; and FU, follow up.

Figure 4. Incremental cost-effectiveness. Computed tomographic angiography (CTA)+CTA vs CTA+no follow-up. Scatter plot of Monte Carlo simulation. Points above the willingness-to-pay (WTP) dashed line indicate lower incremental cost-effectiveness with incremental negative effectiveness from additional procedure complications and greater cost.
to 6 mSv dose of radiation from CTA and the slightly higher dose from DSA.\textsuperscript{6–10} Thus, cancer was not included as a complication in our model.

Cost parameters, especially when not involving a single, direct reimbursement code, have been assigned various values in different studies. Jethwa et al.\textsuperscript{11} assumed a 1.5 multiplier to the cost of an untreated aneurysm relative to that of a treated aneurysm. However, untreated aneurysm portends a much worse prognosis with 80% mortality on rerupture, leading to much higher costs that are difficult to accurately assess. To compensate for the lack of literature values on untreated aneurysm costs, we performed a 1-way sensitivity analysis to vary the costs. Only when cost of an untreated aneurysm exceed a threshold of $1.2 million, CTA+CTA replaces CTA+no follow-up as the optimal strategy.

Our analysis incorporates a comprehensive range of imaging strategies for patients with pSAH on the initial noncontrast CT. By considering all 12 permutations of CTA and DSA for initial and follow-up imaging, our results offer a stronger support for CTA+no follow-up as being the optimal strategy compared with prior papers. Although not performed at our institution, we considered DSA without CTA at initial diagnosis because multiple papers have described this as their imaging strategy for pSAH workup.\textsuperscript{21–25}

The base case scenario simulation shows that CTA+no follow-up has a strict dominance (the highest cost-effectiveness) over all other strategies, with the highest expected utility and lowest cost. DSA, even without accounting for complications, costs >10x as much as CTA. Despite being the reference standard, the 100% sensitivity and specificity assigned to DSA are not realistic. Even assuming 100% sensitivity, the costs associated with the 10x greater complication rate from being an invasive procedure could not overcome the marginally greater sensitivity and specificity. Given the low rate of false negative CTA results, the chance of harboring an aneurysm after a negative initial CTA in patients with pSAH is much smaller than the risk of DSA.\textsuperscript{26}

One-way sensitivity analysis shows that when the sensitivity of the initial CTA is >97.9%, CTA with no follow-up is the optimal imaging strategy. When lower sensitivities are assigned to the initial CTA, CTA+CTA is the optimal strategy. DSA, whether at initial diagnosis or as part of follow-up imaging, is never the optimal strategy in our model.

A Monte Carlo simulation based on CTA sensitivity and specificity of 99.2% shows that even at a WTP threshold of $1 million, CTA+no follow-up is still the best strategy. The additional benefit of the next best strategy, CTA+CTA is primarily attributed to the ability of a repeated CTA to eliminate false negative result from the initial study. A meta-analysis of 50 studies, pooling >4000 patients, shows that rather than repeating the actual study, reinterpretation by a second reader achieves similar results and avoids procedure complications.\textsuperscript{26}

A limitation of this model would be the costs assigned to DSA and CTA according to the US Medicare reimbursement values because it tends to be a lower estimate than the actual costs incurred to the patients or providers/hospitals. However, it is a standard practice to use Medicare reimbursement values in most cost-effectiveness analyses and is recommended by guidelines.\textsuperscript{27–30} Out-of-pocket expenses do not truly reflect the costs of procedures according to World Health Organization guidelines.\textsuperscript{31} In addition, the purpose of a cost-effectiveness analysis is not to calculate the exact costs incurred by each strategy but a relative comparison to aid in clinical decision-making.

**Summary**

CTA without follow-up imaging is the most cost-effective strategy for evaluation of patients with pSAH when modern CT scanners and a strict definition of pSAH are used. DSA and follow-up imaging can be considered on a per-case basis but are not optimal based on our retrospective meta-analysis and mathematical modeling.

**Disclosures**

None.

**References**


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Table I Values and Distributions of Parameters

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<th>Variable</th>
<th>Description</th>
<th>Value</th>
<th>Distribution</th>
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<td><strong>Probabilities</strong></td>
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<td>Incidence of Posterior circulation aneurysms</td>
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<td>Sensitivity of first CTA</td>
<td>0.992(^2)</td>
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<td>Specificity of first CTA</td>
<td>0.992(^2)</td>
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<td>pAllergy_Severe</td>
<td>Incidence of severe allergic-like reaction</td>
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<td>pDSA_Hematoma</td>
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<td>pDSA_TIA</td>
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<td>pDSA_Death</td>
<td>Incidence of DSA-induced death</td>
<td>0.0005(^10)</td>
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<tr>
<td>pCTA_Nephropathy</td>
<td>Incidence of CTA contrast-induced nephropathy</td>
<td>0.0002(^10)</td>
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<td>Incidence of DSA contrast-induced nephropathy</td>
<td>0.0002&lt;sup&gt;10&lt;/sup&gt;</td>
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</tr>
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</table>
| pGood_TreatedAneurysm | Probability of good outcome after treated aneurysm | Mean: 0.7285, Standard deviation: 0.04879<sup>11</sup> | Beta  
| pPoor_TreatedAneurysm | Probability of poor outcome after treated aneurysm | Mean: 0.01805, Standard deviation: 0.0346<sup>11</sup> | Beta  
| pGood_UntreatedAneurysm | Probability of good outcome after untreated aneurysm | Mean: 0.296, Standard deviation: 0.075<sup>11</sup> | Beta  
| pPoor_UntreatedAneurysm | Probability of poor outcome after untreated aneurysm | Mean: 0.0715, Standard deviation: 0.02068<sup>11</sup> | Beta  

**Costs**

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<tr>
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<td>--------------------</td>
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<td>cHematoma</td>
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<td>cTIA</td>
<td>Cost of transient ischemic attack</td>
<td>6318</td>
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<td>cStroke</td>
<td>Cost of stroke</td>
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<td>cNephropathy</td>
<td>Cost of contrast-induced nephropathy</td>
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<tr>
<td>cTreatedAneurysm</td>
<td>Cost of a detected aneurysm</td>
<td>Mean: 22817&lt;sup&gt;16&lt;/sup&gt;</td>
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<td>Standard deviation: 2281.7</td>
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### Utilities

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<th>uGood</th>
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<th>0.6 – 1.0&lt;sup&gt;17&lt;/sup&gt;</th>
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<td>uPoor</td>
<td>Utility of a poor outcome</td>
<td>0.2 – 0.5&lt;sup&gt;17&lt;/sup&gt;</td>
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<td>uDeath</td>
<td>Utility of death</td>
<td>0</td>
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Figure I Sample Subtree of Complications
References for Table I:


