Subtraction CT angiography for the detection of intracranial aneurysms: A meta-analysis

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Received September 25, 2014; Accepted August 10, 2015

DOI: 10.3892/etm.2016.3166

Abstract. The aim of this meta-analysis was to investigate the accuracy of subtraction computed tomography angiography (CTA) for diagnosing intracranial aneurysms. A systematic literature search up to January 1, 2013 was performed in PubMed. Two independent reviewers selected 8 studies that compared subtraction CTA with digital subtraction angiography. Data from the studies were used to construct a 2x2 contingency table on a per-patient basis in ≥5 diseased and 5 non-diseased patients, with additional data on a per-aneurysm basis. Overall, subtraction CTA had a pooled sensitivity of 99% [95% confidence interval (CI), 95-100%] and specificity of 94% (95% CI, 86-97%) for detecting and ruling out cerebral aneurysms, respectively, on a per-patient basis. On a per-aneurysm basis, the pooled sensitivity was 96% (95% CI, 90-99%), and the specificity was 91% (95% CI, 85-95%). In conclusion, subtraction CTA is a highly sensitive, specific and minimally invasive method for the diagnosis and evaluation of intracranial aneurysms.

Introduction

The prevalence of cerebral aneurysm in the general population is estimated to be 1-5% (1). Ruptured intracranial aneurysms are the most important cause of non-traumatic subarachnoid hemorrhage, which is a medical emergency and can result in severe disability or mortality (2). Thus, the prompt diagnosis and treatment of intracranial aneurysm are of considerable importance for the outcome of the patient.

Conventional digital subtraction angiography (DSA) has been considered the gold standard for the detection and characterization of intracranial aneurysms due to its high spatial resolution and large field of view (3,4); however, it also has several disadvantages, including the relatively high cost and the high skill level required to perform the procedure. Furthermore, DSA is an invasive procedure associated with a small but definite risk of neurological morbidity (5). There is a requirement, therefore, to find an accurate, minimally invasive imaging method that is free from these complications. Computed tomography angiography (CTA), as a relatively non-invasive imaging method, has been widely used in the screening of patients with suspected intracranial aneurysms (6). As a result of the rapid improvement in multi-detector CTA technology, the diagnostic performance of multi-detector CTA for the detection of intracranial aneurysms is now approaching that of DSA (7); however, it exhibits a disadvantage in the detection of small-sized aneurysms that are located near the skull base due to the influence of overprojecting bone structures (8).

As CT technology has evolved and various subtraction and post-processing techniques have been developed, subtraction CTA, allowing bone-free visualization of aneurysms, has become possible for the diagnosis of intracranial aneurysms. There have been several reports on the potential usefulness of subtraction CTA in evaluating intracranial aneurysms; however, the results of these studies have been varied (6-8). The purpose of this meta-analysis was to calculate the sensitivity and specificity of subtraction CTA for the detection of cerebral aneurysms, in comparison with the reference standard of DSA.

Materials and methods

Search strategy. A systematic literature search up to January 1, 2013 was conducted in PubMed to identify any relevant studies. The search terms included ‘tomography, X-ray computed’ or ‘computed tomography angiography’, combined with ‘intracranial aneurysm’ or ‘subarachnoid hemorrhage’. Studies that were evidently irrelevant, based on a scan of the titles and abstracts, were excluded, while the remaining articles were assessed for relevance to the topic of interest by reading the full text. Furthermore, a manual search was conducted by checking
the references of retrieved articles to find any additional published studies. All searches were conducted independently by 2 authors, prior to the results being compared. Any questions or discrepancies were resolved through discussion and consensus.

**Study selection.** To be eligible for inclusion in the meta-analysis, the studies had to satisfy 8 inclusion criteria: i) The patients were clinically suspected of having an intracranial aneurysm; ii) the diagnostic index test was bone subtraction CTA; iii) the reference standard was DSA or its combination with neurological findings; iv) the condition of interest was the presence or absence of an intracranial aneurysm; v) 2x2 contingency tables were reconstructed on a per-patient or per-aneurysm basis; vi) the study had no limitations with regard to specific aneurysm types or locations; vii) the study included ≥20 patients, due to the increased likelihood of smaller studies suffering from selection bias; and viii) the study included ≥5 patients with and 5 patients without an aneurysm, so that the study provided meaningful numbers for sensitivity and specificity.

**Data extraction.** The study data were independently extracted by 2 researchers, and any disagreements were resolved through discussion and consensus. The following data were collected: Surname of the first author, year of study publication, country in which the study was performed, study design, age range of the study participants, index test and reference standard. The 2x2 count data were extracted on a per-patient basis and, if reported, on a per-aneurysm basis.

**Assessment of study quality.** Study quality was assessed independently by 2 researchers using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool, which includes 14 quality items (9); disagreement was resolved by consensus. This evidence-based tool was developed to assess the quality of primary studies of diagnostic accuracy. The QUADAS item 4 was scored positive if the delay between the index and reference tests was ≤3 days in all patients. For each study, a quality score was accumulated by assigning 1 point for each QUADAS item if fulfilled, 0.5 if unclear and 0 if not fulfilled. A score between 11 and 14 points was considered high quality and a score ≤11 points as low quality. A more detailed description of each item, together with a guide on how to score each item, is provided in the study by Whiting et al (9).

**Statistical analysis.** For all studies included in the meta-analysis, the individual sensitivities and specificities were recalculated from the 2x2 count data on a per-patient or per-aneurysm basis. Pooled summary estimates were obtained from a bivariate, mixed-effects, binary regression modeling framework. Model specification, estimation and prediction were performed with Stata software, version 11.0 (Stata Corp, College Station, TX, USA). A forest plot was generated that contained the individual study sensitivities and specificities with 95% confidence intervals (CIs) and the pooled sensitivity and specificity estimates. The areas under the receiver operating characteristic (ROC) curves (AUCs) were used to analyze the diagnostic precision.

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**Results**

**Literature search.** The initial search strategy retrieved a total of 5,224 citations. Following the screening of the titles and abstracts, 5,209 sources were excluded. The full texts of the remaining 15 sources were evaluated. Of these, 7 sources were excluded for reasons given in Fig. 1 (13-19). The remaining 8 studies were included (20-27).

The study characteristics are shown in Table I. The quality assessment scores ranged from 10.5 to 13.5, with a median study quality score of 12.5. Four studies were prospective, 2 studies were retrospective, and in 2 studies this was unclear. The 8 studies included 982 patients. Optional count data on a per-aneurysm basis in addition to count data on a per-patient basis were provided by all 8 studies (Table I).

**Assessment of publication bias.** On a per-patient and per-aneurysm basis, the funnel plot and regression test showed no significant publication bias (P=0.30 and P=0.53) (Fig. 2). This suggested that there were no smaller studies with lower diagnostic accuracies that had not been published.

**Analysis of heterogeneity and pooled sensitivity and specificity on a per-patient basis.** The sensitivities ranged from 86 to 100% (Table II). Concerning sensitivity, the selected studies showed moderate heterogeneity (I²=81.2%). For specificity, low heterogeneity was observed (I²=36.0%); the specificity ranged from 89 to 100%. The overall pooled sensitivity was 99% (95% CI, 95-100%), and the pooled specificity was 94% (95% CI, 86-97%) (Fig. 3). The AUC was 0.99 (95% CI, 0.97-0.99) (Fig. 4).

A Spearman rank correlation was performed as a further test for the threshold effect and was determined to be 0.558
which indicated that there was an absence of a notable threshold effect in the accuracy estimates among the individual studies.

The results of meta-regression indicated that the year the study was published, study design, quality score and blinding method were strongly associated with sensitivity, but not with specificity (Fig. 5).

Analysis of heterogeneity and pooled sensitivity and specificity on a per-aneurysm basis. The sensitivities ranged from 77 to 100% (Table II). Concerning sensitivity, the selected studies showed moderate heterogeneity ($I^2=84.3\%$). For specificity, low heterogeneity was observed ($I^2=6.9\%$); the specificity ranged from 86 to 100%. The overall pooled sensitivity was 96% (95% CI, 90-99%), and the pooled specificity was 91% (95% CI, 85-95%). The AUC was 0.96 (95% CI, 0.94-0.97).

Table I. Studies included in the meta-analysis.

<table>
<thead>
<tr>
<th>First author (ref.)</th>
<th>Year</th>
<th>Country</th>
<th>Design</th>
<th>No. of patients</th>
<th>Age, years</th>
<th>QUADAS score</th>
<th>No. of detector rows</th>
<th>RS</th>
<th>No. of aneurysms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jayaraman (20)</td>
<td>2004</td>
<td>US</td>
<td>P</td>
<td>35</td>
<td>54</td>
<td>13.5</td>
<td>Multi-detector</td>
<td>DSA</td>
<td>26</td>
</tr>
<tr>
<td>Yoon (21)</td>
<td>2007</td>
<td>Korea</td>
<td>P</td>
<td>85</td>
<td>49.6</td>
<td>13.5</td>
<td>16</td>
<td>DSA</td>
<td>93</td>
</tr>
<tr>
<td>Romijn (22)</td>
<td>2008</td>
<td>Netherlands</td>
<td>NR</td>
<td>108</td>
<td>56</td>
<td>12.0</td>
<td>4</td>
<td>DSA</td>
<td>117</td>
</tr>
<tr>
<td>Li (23)</td>
<td>2009</td>
<td>China</td>
<td>P</td>
<td>76</td>
<td>48.0</td>
<td>12.5</td>
<td>64</td>
<td>DSA</td>
<td>76</td>
</tr>
<tr>
<td>Zhang (24)</td>
<td>2010</td>
<td>China</td>
<td>P</td>
<td>61</td>
<td>52.0</td>
<td>11.5</td>
<td>Dual-source</td>
<td>DSA</td>
<td>47</td>
</tr>
<tr>
<td>Ramasundara (25)</td>
<td>2010</td>
<td>Australia</td>
<td>R</td>
<td>36</td>
<td>NA</td>
<td>10.5</td>
<td>16/64</td>
<td>DSA</td>
<td>34</td>
</tr>
<tr>
<td>Luo (26)</td>
<td>2012</td>
<td>China</td>
<td>NR</td>
<td>56</td>
<td>48.0</td>
<td>12.5</td>
<td>320</td>
<td>DSA</td>
<td>51</td>
</tr>
<tr>
<td>Lu (27)</td>
<td>2012</td>
<td>China</td>
<td>R</td>
<td>525</td>
<td>52.0</td>
<td>13.5</td>
<td>Dual-source</td>
<td>3D DSA</td>
<td>459</td>
</tr>
</tbody>
</table>

NR, not reported; P, prospective; R, retrospective; QUADAS, Quality Assessment of Diagnostic Accuracy Studies; DSA, digital subtraction angiography; 3D, three-dimensional; RS, reference standard. Data are presented as the mean.

Figure 1. Flow diagram of study identification. ICA, internal carotid artery.

Figure 2. Deeks funnel plot asymmetry test ($P=0.151$) showing log odds ratios on inverse root of ESS for the visualization of publication bias. ESS, effective sample size.
A Spearman rank correlation was performed as a further test for the threshold effect and was determined to be 0.548 (P=0.160), which indicated that there was an absence of a notable threshold effect in the accuracy estimates among the individual studies.

**False-negative CTA results.** Forty-three intracranial aneurysms were missed at subtraction CTA. The location of the false-negative aneurysm was specified for 37 aneurysms (Table III). The size of the false-negative aneurysms was also provided in 37 cases: 19 were <3 mm, 15 were <5 mm and 3 were 5-10 mm in diameter. At least 22 of the missed aneurysms could be detected retrospectively.

**Discussion**

To the best of our knowledge, this study is the first meta-analysis of the diagnostic performance of subtraction CTA to detect cerebral aneurysms. The results show that subtraction CTA has a high diagnostic value for the detection of intracranial aneurysms. According to this meta-analysis of 8 studies, subtraction CTA has an overall sensitivity of ~99% (95% CI, 95-100%) and a high specificity of ~94% (95% CI, 86-97%) for diagnosing cerebral aneurysms on a per-patient basis. On a per-aneurysm basis, the diagnostic accuracy was only slightly lower.

Among the studies included in this meta-analysis, a total of 22 false-negative aneurysms at CTA could be identified retrospectively (20,21,23,24). These false-negative interpretations can therefore be categorized as perceptual in nature and could have been substantially bypassed by double reading.
The $I^2$ statistic for sensitivity indicated the presence of notable heterogeneity, a finding that is consistent with previous meta-analyses investigating CTA and cerebral aneurysms (7,28). The Spearman correlation coefficient on a per-patient basis was 0.558 (P=0.151), which suggested the absence of a significant threshold effect. To determine whether other sources of heterogeneity existed, in addition to the threshold effect, a subgroup analysis was conducted to identify factors affecting heterogeneity. The results of the meta-regression showed that the year the study was published,
study design, quality score and blinding method had a strong association with sensitivity.

Non-subtraction multi-detector CTA has a relatively high sensitivity and specificity for the detection of cerebral aneurysms (6-8); however, the detection of aneurysms adjacent to bone remains a challenging issue due to overlying bone structures. To potentially circumvent this limitation, a number of bone removal techniques, including subtraction and manual or automated bone editing, have been developed; however, these methods are associated with several disadvantages, such as the complexity of use, dependence on the user and the high dose of radiation. Manual bone editing in CTA is a time-consuming and user-dependent process that relies on a knowledge of vascular anatomy (13,14). Matched mask bone elimination (MMBE) is a relatively new technique that enables bone removal in an automatic and user-independent way (18,22). In CTA-MMBE, a second, non-enhanced scan is necessary for the identification of bony structures that could be masked in the CTA scan. The two consecutive volumetric scans expose the patient to more radiation, although low-dose CT techniques are used in the non-enhanced CT. Dual-energy CTA is an immediate automatic bone removal CTA technique that offers the advantage that images from a single CT acquisition can be used to remove bone structures. This technique enables simultaneous dual-energy image acquisition in the same phase of contrast enhancement, which reduces the radiation dose. The limitation of dual-energy CT is that it is not widely available and it requires more expensive hardware (24).

A number of factors should be taken into consideration in the interpretation of the present results. First, homogeneity tests revealed moderate heterogeneity in the sensitivity of the selected studies. The potential sources of variability among the studies were variations in the quality scores, the year that the study was published, the study design and the blinding method used. Secondly, 3 studies were excluded due to the data not enabling the reconstruction of the required 2x2 count tables. It is also possible that the search of the literature did not identify all the eligible studies, but the random omission of studies is less likely to have caused a systematic bias. Although no significant publication bias was suggested by the funnel plot and regression test, unreported publication bias may still have been present. Thirdly, the included studies were limited to populations with a high disease prevalence. The extrapolation of the results of the meta-analysis to screening populations with a disease prevalence that is inherently lower could introduce bias. Finally, the number of studies included in this meta-analysis was relatively small; however, in a previous systematic review (29) investigating the characteristics of meta-analyses and their included studies in the Cochrane Database, it was revealed that, irrespective of the medical field, relatively few studies are typically eligible for meta-analysis for all outcomes and interventions covered by the Cochrane reviews. Furthermore, the methodological quality of the studies included in a meta-analysis has a greater impact on the estimated effects than the numbers of included studies (30,31). QUADAS assessment revealed a high overall quality of the studies included in the present meta-analysis. In conclusion, the results of this study show that subtraction CTA is a highly sensitive, specific and non-invasive imaging method for the diagnosis and evaluation of intracranial aneurysms.

References


