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# Meta-analysis of recent literature on utility of follow-up imaging in isolated perimesencephalic hemorrhage

Bertie Geng[a], Xiao Wu[a], Alexandria Brackett[b], Ajay Malhotra[c,*]

[a] Department of Radiology and Biomedical Imaging, Yale School of Medicine, Box 208042, Tompkins East 2, 333 Cedar St, New Haven, CT, 06520-8042, United States
[b] Research and Education Librarian for the Department of Radiology and Biomedical Imaging Harvey Cushing/John Hay Whitney Medical Library, Yale University, United States
[c] Department of Radiology and Biomedical Imaging, Yale School of Medicine, Box 208042, Tompkins East 2, 333 Cedar St, New Haven, CT, 06520-8042, United States

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ABSTRACT

*Objectives:* Isolated perimesencephalic subarachnoid hemorrhage is an uncommon, distinct subtype of subarachnoid hemorrhage with a more benign prognosis. A negative computed tomographic angiogram has been shown to be reliable in excluding aneurysmal rupture as the underlying etiology. However, some studies continue advocating for more imaging to determine a vascular cause in perimesencephalic subarachnoid hemorrhage. The objective of this study is to evaluate the evidence for use and utility of repeat angiographic imaging after a negative computed tomographic angiogram in patients with perimesencephalic subarachnoid hemorrhage.

*Patients and methods:* Retrospective institutional analysis of patients with perimesencephalic subarachnoid hemorrhage was performed from 2014 to 2017 for number and types of follow-up angiographic imaging studies performed. Updated meta-analysis of literature was performed from 2014 onwards to assess the utility of follow-up imaging after a negative initial angiographic study.

*Results:* The institutional review revealed no utility of additional imaging after a negative computed tomographic angiogram in 6 patients with isolated perimesencephalic subarachnoid hemorrhage. Literature review and metaanalysis of 13 studies with 588 patients revealed a vascular etiology in 3 patients with isolated perimesencephalic subarachnoid hemorrhage from a single study- 2 aneurysms and 1 patient with vasculitis.

*Conclusions:* Use of repeat angiographic imaging after a negative computed tomographic angiogram for perimesencephalic subarachnoid hemorrhage patients remains not uncommon, despite previous meta-analysis. Review of the more recent literature is consistent with previously published meta-analysis and shows limited benefits despite frequent use. In patients with a strictly defined perimesencephalic subarachnoid hemorrhage pattern and clinical picture consistent with perimesencephalic subarachnoid hemorrhage, an initial negative computed tomographic angiogram should be adequate and repeated follow-up studies can be avoided.

## 1. Introduction

Perimesencephalic subarachnoid hemorrhage (pSAH) represents a distinct subtype of SAH patients with hemorrhage centered in the perimesencephalic cisterns. It is uncommon with an incidence of 0.5/100,000 patients [1]. It has a more benign clinical course compared to diffuse SAH caused by aneurysmal rupture [2–4]. Up to 12% of posterior circulation aneurysms can present with a perimesencephalic pattern of blood [5]. Angiographic imaging is needed due to lack of sensitive and specific clinical or imaging features to distinguish aneurysmal from nonaneurysmal cases [6]. Computed tomographic angiogram (CTA) has been shown to be reliable for excluding aneurysms in pSAH. There is debate on the utility of digital subtraction angiography (DSA) and subsequent angiographic imaging [7–9]. In a previous meta-analysis in 2014, based on 1031 patients who met strict imaging criteria of pSAH in 40 studies, we found only 8 reported aneurysms that were detected on subsequent imaging after a negative CTA, some with questionable validity [10]. However, multiple studies have been published since in the last 3 years, with some still advocating further imaging after a negative CTA for pSAH patients [11].

We undertook this study to conduct an updated meta-analysis of the literature in the last 3 years to assess the utility of further imaging for

* Corresponding author.
*E-mail addresses:* bertie.geng@yale.edu (B. Geng), xiao.wu@yale.edu (X. Wu), alexandria.brackett@yale.edu (A. Brackett), ajay.malhotra@yale.edu (A. Malhotra).

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aneurysm detection in pSAH after a negative initial angiographic study. We also performed a retrospective review of institutional patients in the last 3 years to evaluate the impact on practice patterns of the previous review.

## 2. Patient and methods

### 2.1. Institutional study

We performed a retrospective keyword search of the radiology imagining database at our single, large, academic institution after obtaining approval from Institutional Review Board with waiver of consent, using the phrase "perimesencephalic," "prepontine," or "pretruncal" hemorrhage from 2014 to 2017. Patients were eligible for inclusion if they demonstrated a perimesencephalic pattern of hemorrhage on initial noncontrast CT and underwent CTA imagining with 24 h of admission with later additional follow up angiographic imaging. Exclusion criteria included patients with a history of trauma or non-perimesencephalic distribution of SAH. A neuro-radiologist reviewed associated images of reports with relevant keywords to determine if the hemorrhage pattern met inclusion criteria for pSAH. Follow-up imaging was reviewed for intracranial aneurysms and other possible causes of pSAH.

All CTA examinations were performed on 64-section multidetector CT scanners (General Electric Lightspeed, Milwaukee, WI) using standard protocol. Scanning was performed from the base of C2 to the calvarial vertex. Intravenous contrast, iohexol (Omnipaque 300/350; Nycomed Amersham, Oslo, Norway), was administered by using a dual-power injector with an injection rate of 4 mL/s for a total volume of 60 mL for Omnipaque 350 and 75 mL for Omnipaque 300 and then followed by a saline chaser of 80 mL. The SmartPrep technique (GE Healthcare, Milwaukee, WI) was used to adequately time the bolus of contrast. The protocol for data acquisition was helical mode, 0.5-s gantry rotation time, 32 × 0.625-mm collimation, 0.5 to 1 pitch, 0.625-mm section thickness, and 0.315-mm reconstruction interval. Acquisition parameters were 100 to 120 kV and 300 to 660 mA, a head filter with a display field of view of 15 cm, and a standard reconstruction algorithm. Images were reformatted in axial, sagittal, and coronal 2.5-mm-thick maximum intensity projections with 50% overlap, as well as 3-dimensional (3D) surface-rendered and volume-rendered reconstructions, using Advantage Workstation (GE Healthcare) and Vitrea 2 workstation (Vital Images, Plymouth, MA).

DSA was performed by using a single dedicated biplane neuroangiographic unit (Siemens Axiom Artis zee; Siemens, Erlangen, Germany) with an image intensifier matrix of 1024 × 1024 pixels. Cerebral angiography included rotational spin angiography with 3D reconstructions (DynaCT; Siemens, Erlangen, Germany).

### 2.2. Meta-analysis

#### 2.2.1. Data sources

A medical librarian conducted the search with the peer-review of another librarian. The search was generated using the original meta-analysis article [10]. Search terms were updated and added after reconsidering the current breadth of the topic. Terms were agreed on after a consultation meeting with the lead authors. The original article also was used to validate the search, before limiting the results to 2014 to current. The date limiters were added since this search would help inform the impact of the original article. No other limiters were used. The databases were searched on July 21, 2017; the databases include: OVID Medline, OVID Embase, Web of Science, PubMed, and Cochrane. See online supplement for the full search strategies.

The final search found a total of 448 records with 65 original articles. These results were exported into EndNote, where they were dedupliated, and then uploaded to Covidence for screening.

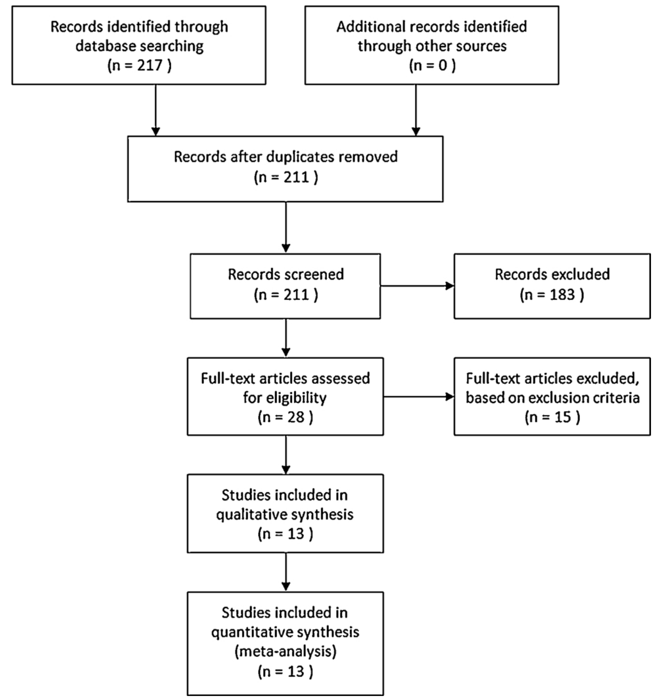


**Fig. 1.** PRISMA flowchart.

#### 2.2.2. Study selection

The study protocol was registered with the PROSPERO international prospective register of systematic reviews on 6/19/2017 (Registration number: CRD42017068544) Two separate screeners (AM, BG) evaluated the titles, abstracts and full text of the eligible articles. When evaluations differed, the two reviewers reexamined the articles together to reach a consensus. Full length papers, poster presentations, and oral presentations were eligible for inclusion if they reported follow up imaging for pSAH after an initially negative CTA or DSA. Abstracts were included if a full manuscript or presentation was unavailable. Papers including participants of all ages were included. Studies that did not focus exclusively on pSAH were included if the paper provided relevant information on the pSAH subgroup specifically. Review articles, case reports, papers that were included in the previous analysis [10] and full articles or presentations that were unavailable in English were excluded. A flowchart of the search flowchart is presented in Fig. 1 accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

#### 2.2.3. Data extraction and quality assessment

One reviewer extracted data of interest from the publications, initial angiography method (DSA or CTA), follow up angiography method, time of follow up angiography, and yield of initial and follow up angiography, including any possible sources of hemorrhage. Patient age and gender were only recorded if this information was available for the subgroup of patients specifically presenting with pSAH. A second author reviewed the extracted data for accuracy.

Two authors (AM, BG) independently evaluated the quality of each article included into the study using the Quality Assessment of Diagnostic Accuracy Studies Tool (QUADAS-2) criteria [12]. When assessments differed, the two authors re-examined the study together and reached a consensus.

#### 2.2.4. Data synthesis

Mean and standard deviations were generated using Excel (Microsoft, Redmond, WA). Patient mean ages and standard deviations were calculated only from papers that reported this demographic information specifically for the pSAH subgroup. A forest plot was generated using RStudio (RStudio, Boston, MA) with an event defined as the number of patients with a source of hemorrhage newly identified on repeat angiographic imaging (DSA or CTA) and total defined as the total number of patients who underwent repeat angiography (DSA or CTA) after an initial angiography (DSA or CTA) failed to demonstrate a source of hemorrhage. A funnel plot was generated and Egger's p-value was calculated using RStudio.

## 3. Results

### 3.1. Institutional study

Eight CT reports met the keyword search criteria and after review by a neuro-radiologist 2 were excluded- one patient had a history of trauma, and the second patient had subdural hemorrhage in addition to pSAH. 6 patients had isolated, non-traumatic pSAH pattern of hemorrhage and were included in the study. Four women and two men had a mean age of 46.2 ± 19.1 years. All patients had initial negative CTA, and all but one patient had initially negative DSA as well (one patient never received DSA imaging). A total of 20 CTAs, 10 MRI/MRA/MRV, and 5 DSAs were performed on these 6 patients for an average of 3.33 CTAs, 1.67 MRI/MRA/MRVs, and 0.83 DSAs per patient. The patient who received the most imaging was a 31 year old female who received 1 DSA, 4 CTAs, and 4 MRI/MRA/MRVs. The patient who received the least imaging was a 45 year old female who received 1 DSA, 2 CTAs, and 1 MRI/MRA/MRV. No vascular lesions or cause of hemorrhage was identified on any of the follow-up imaging performed. No patients had clinically significant hydrocephalus.

### 3.2. Meta-analysis

Out of 211 screened abstracts, 28 abstracts were included for full text screening. Of those 28 full length reports, 13 met inclusion criteria. These 13 reports included 686 patients with an average age of 53.32 and a male to female ratio of 57.0:43.0 (Table 1). Of these 686 patients, 685 patients had initially negative DSA or CTA and 588 of patients with initially negative angiography results had follow up imaging with DSA, CTA or both. Out of these 588 patients, an intracranial aneurysm or other cause of hemorrhage was identified in three patients. The Forest plot is included in Fig. 2. This is a rate of 0.10% (95% CI: 0/00%-0.81%) of detection of the cause of hemorrhage on follow-up imaging weighted by the study population in each included study (Fig. 2). The $I^2$ was 0% for the meta-analysis, indicating low heterogeneity among the included studies. The Funnel plot is included in Fig. 3 and the Egger's linear regression p-value was 0.3865, not significant for asymmetry.

#### 3.2.1. Study quality and strength of evidence

Some studies had important concerns regarding their validity (online supplemental Table 1). Some had high risk of bias because patients did not undergo the reference standard DSA. An important applicability concern is that 30.8% of studies did not state the criteria used to define pSAH. Overall, the strength of evidence was of good quality for rates of discovery of the cause of hemorrhage on second imaging (online supplemental Figure 6).

## 4. Discussion

The use of additional angiographic imaging in patients with perimesencephalic SAH after a negative initial CTA remains common, with limited utility. In a previous 2014 meta-analysis looking at 1031 patients in 40 included studies, we found 6 studies with 8 aneurysms found only on follow-up imaging, most of them of questionable validity. The 16 institutional pSAH patients in that study also did not reveal a vascular etiology of hemorrhage on follow-up imaging.

The 6 institutional patients with pSAH between 2014–2017, since the publication of the previous metaanalysis, did not have any appreciable difference in the extensive imaging follow-up after negative initial CTA, without additional utility. On the updated review of literature since 2014, we found 13 additional studies with 588 patients that matched the inclusion criteria. A vascular etiology was reported in 3/588 patients - aneurysm was found in 2 patients and vasculitis in a third patient in the study by Heit et al. The other 12/13 studies with 517 patients reported no vascular etiology, thereby questioning the utility of further additional imaging. The pooled detection rate of aneurysm on follow-up studies was 0.10% (95% CI: 0 – 0.81%) weighted by the population in each study. This is even lower than the 0.78% we found in the previous analysis of literature until 2014 [10].

Heit et al in 2016 recommended that all patients presenting with CTA negative for perimesencephalic SAH continue to undergo DSA [11]. This was based on a retrospective review of 71 cases of pSAH seen over a 11-year period which revealed 2 aneurysms and 1 case of vasculitis/vasculopathy, not seen on initial CTA. Details about the 2 positive aneurysm cases were not provided but one of the provided images (Fig. 3 in Heit et al.) showed an irregular, dissecting supraclinoid ICA aneurysm detected on DSA performed at 7 days. However, in the images provided, the bolus and technique (magnification) seem different between intial and follow-up study, and a questionable focus can be seen on initial imaging after reviewing the follow-up DSA [13].

We found similar reports of negative CTA and aneurysms found on subsequent DSA in the previous meta-analysis. While Ringelstein et al acknowledged that the superior cerebellar artery demonstrated irregularity on the initial study, Delgado et al stated that the aneurysm was not present initially although the images provided were suspicious of abnormality even on initial imaging [14,15].

In the current review, Mortimer et al reported 2 patients with findings on DSA that were not seen on CTA, but commented that the abnormality in each case was of doubtful significance [16]. This included a small A1 bleb felt to be not responsible for pSAH. The second patient had a motion-degraded, poor quality CTA. In their review of the literature, Mortimer et al reported 1 other case in literature of false-negative CTA in the study by Cruz et al in 2011 [17]. However, the 1-mm left ICA aneurysm reported by Cruz et al was not considered to be the source of hemorrhage by the authors themselves.

Controversy regarding use of repeated imaging for pSAH has been long-standing. Rinkel et al in 1991 had suggested that pSAH patients may not need repeat DSA after negative initial DSA [4]. They subsequently suggested that DSA was not needed even initially after a negative CTA [18]. Multiple subsequent studies have since questioned the utility of aggressive imaging in patients with pSAH [8,9]. Studies which have recommended further imaging have either ascribed pSAH to anterior circulation aneurysms or lack adequate retrospective review if the aneurysms could be seen on initial imaging in hindsight [19–21]. The current analysis shows that the use of repeat imaging persists despite literature evidence to thr contrary, as shown by the previous meta-analysis [10]. This may be driven by the fear of missing an aneurysm on the initial study. However, if patients have a strictly defined pattern of pSAH without concerning features, there is limited utility as shown by this updated meta-analysis including 588 patients. We hope this updated literature would be considered for revision of guidelines on management of subarachnoid hemorrahge, which may result in change of practice [22].

CTA has become widely accepted as the initial diagnostic modality because of its wide availability, noninvasive nature, speed, and high resolution images. Modern scanners with 16- and 64- detector rows offer a submillimeter resolution [23]. However, older scanners had lower sensitivity ranging from ranging from 92.3% to 96%, with a 61% sensitivity for ≤3-mm aneurysms [24]. In the only positive study in the current review, Heit et al found 2 aneurysms over an 11-year institutional experience (2002–2012). However, 64 detector scanners did not come into clinical use until 2006 and it is not clear if the negative CTA for the 2 aneurysmal cases were before or after 2006. The sensitivity of CTA has also been shown to be related to arterial attenuation, with

**Table 1**
Patient data and imaging yield in included studies.

| Study, Year | Number of patients (number of women) | Patient age ± standard deviation | Number of patients who received an initial CTA | Initial CTA yield[b] | Number of patients who received an initial DSA | Initial DSA yield | Repeat imaging modality | Number of patients who received repeat imaging | Repeat imaging yield |
|---|---|---|---|---|---|---|---|---|---|
| Akcakaya et al, 2016 [30] | 33 (UR[a]) | UR | | | 33 | 0 | DSA | 33 | 0 |
| Almandoz et al, 2014 [31] | 12 (5) | UR | 12 | 0 | 12 | 0 | CTA or DSA | 12 | 0 |
| Canneti et al, 2015 [32] | 17 (8) | 51.52 ± 9.43 | 15 | 0 | 2 | 0 | DSA | 17 | 0 |
| Coelho et al, 2016 [33] | 29 (16) | 52.4 ± 11.8 | 29 | 0 | | | CTA or DSA | 26 | 0 |
| Heit et al, 2016 [11] | 71 (33) | UR | 71 | 0 | 71 | 0 | DSA | 71 | 3 |
| Kumar et al, 2014 [34] | 22 (7) | 52.45 | 22 | 0 | 22 | 0 | DSA | 22 | 0 |
| Mortimer et al, 2016 [16] | 72 (24) | 52.7 ± 10.8 | 72 | 0 | | | DSA | 72 | 0 |
| Potter et al, 2016 [35] | 131 (53) | 53 | | | 131 | 0 | DSA | 131 | 0 |
| Sahin et al, 2016 [36] | 24 (12) | 53 ± 12 | | | 24 | 1 | DSA | 22 | |
| Song et al, 2017 [37] | 62 (UR) | UR | | | 62 | 0 | CTA or DSA | 45 | 0 |
| Woodfield et al, 2014 [38] | 90 (UR) | UR | 90 | 0 | 90 | 0 | DSA | 20 | 0 |
| Xu et al, 2017 [39] | 82 (40) | 55.4 ± 9.6 | 82 | 0 | 82 | 0 | DSA | 82 | 0 |
| Yap et al, 2015 [40] | 41 (UR) | UR | 39 | 0 | 2 | 0 | DSA | 35 | 0 |

[a] UR = unreported.
[b] Yield is defined as finding underlying cause for the pSAH on imaging.

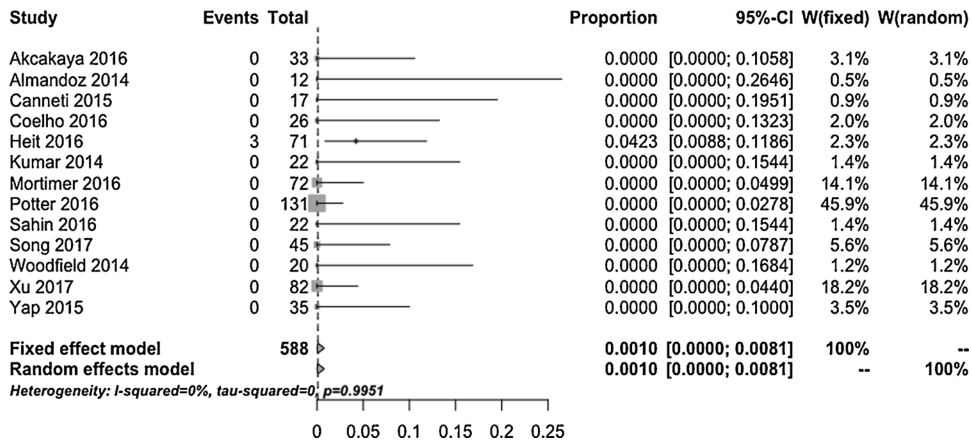


**Fig. 2.** Forest plot of discovery rates of the cause of pSAH on repeat imagining.

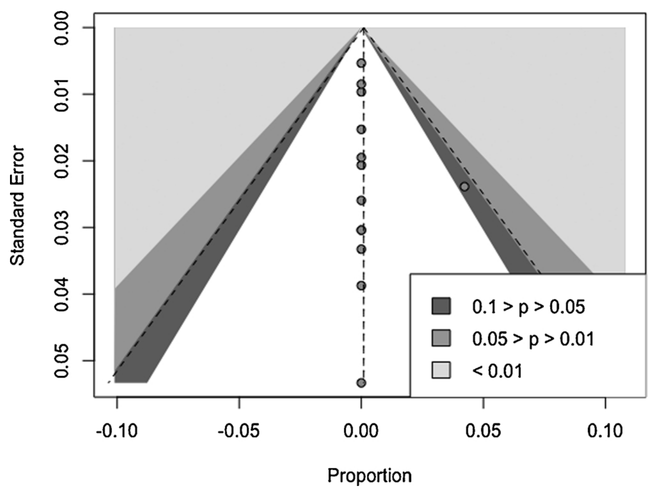


**Fig. 3.** Funnel plot of standard error and discovery rates of the cause of pSAH on repeat imaging.

significant difference between true positive and negative cases (mean 535 ± 110 HU) compared to false negative cases (mean 424 ± 30 HU) [25]. Suboptimal CTA in isolated cases cannot be a justification for performing repeated angiographic imaging in all patients with pSAH.

Although DSA is touted as the gold-standard, it is operator- and interpretation-dependent. Aneurysms have been reported to be missed even on biplane DSA, seen on subsequent studies [26].

Rebleeding is extremely rare in patients with pSAH. Only a few cases have been reported in the literature [27]. Even after a pSAH recurrence, aneurysmal etiology is not found on repeated imaging. Most patients with pSAH have good outcomes and have a normal life expectancy [2]. Complications such as vasospasm and hydrocephalus are infrequent [28,29].

Repeat, aggressive imaging may not be required in patients with pSAH and is not cost effective [30]. Conventional angiography and repeat imaging carry complications as well as associated costs. Partial thrombosis and recanalization and growth in a dissecting pseudoaneurysm are potential reasons for missing aneurysms on initial imaging, and

follow-up DSA imaging may be considered on a case-by-case basis, especially in patients with atypical features of pSAH.

## 5. Conclusions

Updated review of the literature and institutional practice reveals continued use of repeat imaging after a negative CTA for pSAH patients, with limited utility. In patients with a strictly defined pSAH pattern and clinical picture consistent with pSAH, an initial negative CTA should be adequate.

## Disclosure

None for all authors.

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## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.clineuro.2019.03.006.

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