CT angiogram negative perimesencephalic subarachnoid hemorrhage

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CT angiogram negative perimesencephalic subarachnoid haemorrhage: Is a subsequent DSA necessary? A systematic review

Authors and affiliations:

Midhun Mohan ¹*, ORCID ID: 0000-0002-1865-8623
Abdurrahman I. Islim ^{2, 3}*, ORCID ID: 0000-0001-9621-043X
Louise Dulhanty ¹, ORCID ID: 0000-0003-2995-1187
Adrian Parry-Jones ^{1, 4}, ORCID ID: 0000-0002-4462-3846
Hiren C. Patel ^{1, 4}, ORCID ID: 0000-0002-1439-8801

***These authors contributed equally to the manuscript**

¹ Greater Manchester Neurosciences Centre, Salford Royal Foundation NHS Trust, Stott Lane, Salford, M6 8HD
² Institute of Translational Medicine, University of Liverpool, Liverpool, UK
³ Department of Neurosurgery, The Walton Centre NHS Foundation Trust, Liverpool, UK
⁴ Division of Cardiovascular Sciences, School of Medical Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester Academic Health Sciences Centre, Manchester, M13 9PT.

Correspondence:

Mr Hiren C Patel
Greater Manchester Neurosciences Centre
Salford Royal Foundation NHS Trust
Salford
M6 8HD, UK
Email: hiren.patel@srft.nhs.uk
Tel: +44 (0)161 206 8548

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ABSTRACT

Background

Perimesencephalic subarachnoid haemorrhage (PMSAH) is a benign subtype with distinct clinical-radiological features. Digital subtraction angiography (DSA) remains the gold standard investigation for exclusion of a macrovascular cause, although increasingly more clinicians rely solely on computed tomography angiography (CTA). The primary aim of this systematic review was to evaluate the current literature regarding the negative predictive value of CTA.

Methods

A systematic search in concordance with the PRISMA checklist was performed for studies published between 2000 and 2018. Studies with ≥ 10 adult patients diagnosed on a non-contrast brain CT with a PMSAH, who underwent a negative CTA and were subsequently subject to a DSA, were included. Simple pooled analysis was performed to inform the negative predictive value (95% CI) of CTA and risk of DSA- and CTA-related complications.

Results

Eighteen studies (669 patients) were included. All patients were subject to at least one DSA; first one mostly performed within 24 hours of CTA (68.6%). 144 (21.5%) patients underwent a 2nd DSA and a 3rd repeat DSA was performed in one patient. The overall negative predictive value of CTA was 99.0% (95% CI 97.8–99.5). The risk of complications following DSA and CTA were 1.35% (3/222) and 0% (0/41) respectively.

Conclusions

Undertaking a DSA after a negative CTA may not add any further diagnostic value in patients with perimesencephalic subarachnoid haemorrhage and may lead to net harm. This observation needs to be validated in a large-scale prospective multi-centre study with complete case ascertainment and robust data on CTA and DSA complications.

Key words: Computed tomography angiography; Digital subtraction angiography; Perimesencephalic; Subarachnoid haemorrhage; Systematic review.

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INTRODUCTION

Most spontaneous non-traumatic subarachnoid haemorrhage (SAH) is of aneurysmal origin, however, approximately 15% have no discernable cause diagnosed on initial vascular imaging.¹ Of these, 30-60% have a perimesencephalic (PMSAH) pattern of bleed, which is recognised as a distinct clinical entity of SAH, with a benign natural history.^{2 3}

Although there has been some debate about the anatomical definition of PMSAH, its radiographic pattern on timely computed tomography (CT) is relatively distinct with haemorrhage confined anterior to the midbrain or pons. The definition of PMSAH also allows for the extension of blood into the suprasellar cistern or basal portion of the sylvian fissures and intraventricular blood, although requires the absence of frank intraventricular or intraparenchymal haemorrhage.^{4 5}

Currently, the gold standard investigation for diagnosing a vascular lesion responsible for SAH is a digital subtraction angiography (DSA).⁶ However, the risk of DSA-related complications, including persistent neurological deficits is non-negligible, and has been reported to be as high as 14%.^{7 8} Typically, patients with PMSAH are not neurologically obtunded, have early symptom resolution, and rarely have a vascular cause identified on DSA.^{2 3} Because of the high risk of morbidity and mortality associated with a missed macrovascular cause, particularly posterior circulation aneurysms,^{5 9} imaging techniques that are specific, sensitive and non-invasive are essential.

Neurovascular imaging techniques have evolved significantly over the last two decades and the availability of computed tomography angiography (CTA) means that macrovascular causes of brain haemorrhage can be identified without a DSA.^{10 11}

The primary aim of this systematic review was to determine the value of performing a DSA in PMSAH patients that were not found to have a vascular cause of bleed on initial CTA. The secondary aim was to compare the complication risks of CTA and DSA.

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METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement,¹² and has been registered with PROSPERO (CRD42016032349).

Definitions

The following definitions were used throughout this review:

- Patients with a perimesencephalic SAH pattern of bleed were referred to as PMSAH patients.
- PMSAH patients who underwent a CTA as the first vascular investigation and were found to have no cause to explain the bleed, were termed as CTA-negative PMSAH patients.
- CTA-negative PMSAH patients who subsequently underwent a DSA and were found not to have a vascular cause of bleed, were referred to as DSA-negative PMSAH patients.

Search Strategy

A literature search was performed and last updated on July 24, 2018 in:

- Embase (Ovid): 1974 to present
- Medline (Ovid): Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and 1946 to Present
- CINAHL Plus (EBSCO)
- Cochrane Library: Central Register of Controlled Trials

The search strategy used for Embase (Ovid) and Medline (Ovid) can be found in the supplementary material (**online supplementary table 1**). The search strategy was altered appropriately for use in other databases. Bibliographies of all full-text articles screened were examined for additional studies that could have met the inclusion criteria.

Paper selection

The titles of all results were screened independently by two authors (M.M. and A.I.I.). Abstracts were reviewed if titles included the following terms: non-aneurysmal-, CTA negative-, perimesencephalic- or pre-truncal SAH, in combination with DSA, imaging and diagnostic studies or anything of similar construct. Full text articles were obtained for abstracts which alluded to patients being subject to both CTA and DSA. Articles identified were included upon mutual agreement. If disagreements occurred, these were discussed with a senior author (H.C.P.) until consensus was reached. Full text articles were subject to the population, intervention, comparison, outcomes and study design (PICOS) inclusion criteria outlined in

Table 1.

Table 1. PICOS inclusion criteria		
Population	Patients diagnosed on a non-contrast brain CT with a perimesencephalic SAH, who underwent a CTA and were subsequently found not to have a vascular cause to explain the initial bleed. All traumatic SAH were excluded. Patients with a poor Hunt-Hess or the World Federation of Neurosurgical Societies' score (grades IV-V) were excluded	
Intervention	DSA	
Comparator	Not applicable	
Outcomes	Primary	Secondary
	Vascular cause to explain the initial bleed missed on CTA	DSA related complications
		CTA related complications
Study design	Retrospective and prospective cohort studies with ≥10 adult patients (≥ 16 years).	
Abbreviations: CTA=computed tomography angiography; DSA=digital subtraction angiography; SAH=subarachnoid haemorrhage		

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Data extraction

A pre-piloted standardised proforma (**online supplementary figure 1**) was used to extract data independently by two authors (M.M. and A.I.I.). When study cohorts comprised only a subsection with CTA-negative PMSAH patients, the following imputation approach was implemented:

- Studies in which CTA-negative PMSAH patients comprised $\geq 90\%$ of the cohort, weighted averages were calculated for quantitative analysis.
- Data fields with a lower percentage were categorised as not reported.

Data synthesis and statistical analysis

Negative predictive value (NPV), defined as the percentage of patients with a negative test who do not have the disease,¹³ was determined using the following formula: $NPV = \frac{TN}{TN + FN}$. TN True negatives. These are DSA-negative PMSAH patients. FN = False negatives. These are the CTA-negative PMSAH patients who were subsequently found to have a vascular lesion on DSA that could explain the bleed. NPV 95% CI was calculated according to the efficient-score method.¹⁴ Baseline patient demographics were expressed using descriptive statistics. Data were analysed using SPSS version 24.0 (IBM, Armonk, NY, USA).

Quality assessment

All included studies were subject to quality assessment using the Quality Assessment for Diagnostic Accuracy Studies (QUADAS-2) tool (accessed using: <http://www.bristol.ac.uk/population-health-sciences/projects/quadas/quadas-2/>). This was independently performed by two authors (M.M. and A.I.I.). Any discrepancies were discussed with the senior author (H.C.P.) before reaching a consensus.

RESULTS

Literature search

The study selection process is illustrated in **Figure 1**. The total number of titles screened was 181. Of those, 108 abstracts were reviewed and 52 were subsequently excluded. Fifty-six full-text articles were assessed for eligibility and 10 of their references were also examined. The final number of articles included was 18.¹⁵⁻³²

Study characteristics

The characteristics of the 18 included studies are summarised in **Table 2**. The majority were published after 2010. Six were prospective,^{15 22 24-26 32} and one study was multi-centre.¹⁸ Included exams span a 20-year study period, from 1998 to 2017.

Patient demographics and clinical characteristics

The overall number of CTA-negative PMSAH patients was 669 with a study specific range from 10 to 93 patients. Age was reported in 7 studies for a total of 206 (30.8%) patients. The weighted mean age was 52.8 years (SD=3.8). Eleven studies reported sex with 240 males and 172 females. Presenting Glasgow Coma Scale (GCS), available for 127 patients, was 15.

Initial diagnosis of PMSAH on CT brain

Time from symptom onset or ictus to non-contrast CT ranged from 0 (day of admission) to 12 days (4 studies, 151 patients); 125 (82.8%) patients had their CT brain within 3-days of ictus. Gijn et al's definition of a PMSAH was adopted in all studies apart from one⁴⁵. This study did not state the criteria they used to define PMSAH. The CT brain was interpreted and reported by two or more neuroradiologists in 96.5% (219/227 with available data) of patients.

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Table 2. Study characteristics of the 18 included articles								
Study authors	Publication year	Study design	Setting	Study period	N. of CTA negative PMSAH patients	Median/mean age (yrs.)	Female: male	N of PMSAH patients examined by at least one DSA
Huttner at al. ¹⁵	2006	Prospective	SC	2000 - 2004	64	NR	NR	64
Kershenovich et al. ¹⁶	2006	Retrospective	SC	2001 - 2005	11	52.5/52.2	6:4	10
Westerlaan et al. ¹⁷	2007	Retrospective	SC	2003 - 2006	30	NR	NR	30
Agid et al. ¹⁸	2010	Retrospective	MC	2005 - 2009	93	NR	NR	93
Cruz et al. ¹⁹	2011	Retrospective	SC	2006 - 2010	41	NR/49.9	17:24	41
Pechlivanis et al. ²⁰	2011	Retrospective	SC	2002 - 2008	28	NR/60.3	17:11	28
Kelliny et al. ²¹	2011	Retrospective	SC	1998 - 2007	19	NR	NR	19
Delgado Almandoz et al. ³²	2012	Prospective	SC	2005 - 2010	28	NR	16:12	28
MacKinnon et al. ^{22*}	2013	Prospective	SC	2003 - 2011	11	NR	NR	11
Kalra et al. ²³	2014	Retrospective	SC	2008 - 2014	18	NR/49.3	8:10	18

Kumar et al. ²⁴	2014	Prospective	SC	2011 - 2013	20	NR/52.5	6:14	20
Germans et al. ²⁵	2014	Prospective	SC	2009 - 2012	53	52/NR	23:30	52
Yap et al. ²⁶	2015	Prospective	SC	2007 - 2013	39	NR/NR	NR	35
Canneti et al. ²⁷	2015	Retrospective	SC	2002 - 2013	15	NR/51.5	7:8	15
Ramgren et al. ²⁸	2015	Retrospective	SC	2005 - 2015	27	NR/NR	NR	27
Heit et al. ²⁹	2016	Retrospective	SC	2002 - 2012	71	NR	NR	71
Mortimer et al. ³⁰	2016	Retrospective	SC	2006 - 2014	72	NR/52.7	24:48	72
Bashir et al. ^{31†}	2018	Retrospective	SC	2011 - 2017	35	NR/NR	13:22	35
Abbreviations: NR=not reported; SC=single centre; MC=multi-centre								
*Study did not specify the end date of study period. Submission date was used instead								
†5 patients for whom the initial diagnostic test was not clear were excluded								

CTA protocol

Time from ictus to CTA was not available for 87.4% of patients. For those with available data, the time frame ranged from 0 (day of admission) to 17 days. Time from CT to CTA was not available in all studies. Studies which reported a CTA protocol (15 studies), utilised a helical or spiral multi-detector CT scanner. Interpretation of CTA was carried out by one neuroradiologist in 51.4% (196/381 with available data) of patients. The remaining radiology was subject to dual reporting. CTA was reported prior to DSA in 167 patients.

First DSA protocol

Time from CTA to first DSA ranged from 0 (occurring concurrently) to 20 days; with 68.6% (83/121 with available data) of patients having their DSA within 24 hours. DSA was performed in a biplane neuroangiography unit in 78.6% (427/543 with available data) of patients. A 4-vessel DSA was carried out in 237 (35.4%) patients, a 6-vessel DSA in 231 (34.5%) patients whereas in the remaining cohort, the data was not available. A three-dimensional rotational DSA was used in 64.3% (205/319 with available data) of patients. Dual or triple interpretation of DSA by neuroradiologists was undertaken in 72.5% (137/189 with available data) of patients.

Repeat 2nd and 3rd DSA protocol

One hundred and forty-four patients underwent a 2nd DSA. Timing was reported for 51 patients, with 22 undergoing the 2nd DSA after 6 weeks of first DSA. A mean duration of 6.4 days was observed between first and 2nd DSAs in 29 patients. A 3rd repeat DSA was only carried in one patient. Timing was not reported.

Missed vascular abnormalities on initial CTA

A total of 7 (1.05%) abnormalities were found on first or subsequent DSA which were not identified on initial CTA. These are summarised in **Table 3**. The overall NPV was 99.0% (95% CI 97.8 – 99.5).

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Table 3. Missed vascular lesion on initial CTA found subsequently on DSA

	First DSA		Second DSA	
	Vascular lesion		Vascular lesion	
	Definite cause of bleed*	Abnormalities felt not to be the cause of the bleed*	Definite cause of bleed*	Abnormalities felt not to be the cause of the bleed*
Cruz et al. 2011 ¹⁹	-	1-mm left internal carotid artery aneurysm	-	-
Delgado Almandoz et al. 2012 ³²	-	-	2-mm aneurysm arising from a branch of the left superior cerebellar artery [†]	-
Heit et al. 2016 ²⁹	Vasculitis	-	-	-
	Right supra clinoid internal carotid artery aneurysm	-	-	-
	Aneurysm (unspecified)	-	-	-
Mortimer et al. 2016 ³⁰	-	Small A1 anterior cerebral artery bleb [‡]	-	-
	Non-dominant vertebral artery irregularity: atheroma or dissection [†]	-	-	-
Total	4	2	1	0

%	0.59	0.29	0.69	-
NPV (95% CI)	99.4% (98.4 – 99.8)	99.7% (98.8 – 99.9)	99.3% (95.6 – 99.9)	-
	99.1% (98.0 – 99.6)		-	-
	99.0% (97.8 – 99.5)			
Abbreviations: NPV=negative predictive value				
*As stated by study authors				
†Received endovascular treatment				
‡Managed conservatively				
Details regarding management strategies of other abnormalities were not available				

CTA- and DSA-related complications

One study comprising 41 patients reported no complications following CTA. The remaining 17 studies did not report whether CTA complications occurred or not. A total of 811 DSAs were performed across the 18 studies included. For 222 (27.4%) DSAs with available data, 3 (1.35%) complications occurred. One patient suffered from a bilateral posterior cerebral artery infarct leading to visual loss and one patient had left vertebral artery dissection with arterial occlusion. Contrast-related nephrotoxicity was the last complication observed resulting in widespread cerebral edema, hemiparesis and coma, albeit patient recovered afterwards.

Quality and bias assessment

The quality assessment results are summarised in **online supplementary figure 2**. In most studies, there was a low risk of bias regarding selection of patients. However, lack of details surrounding CTA protocols and timing of DSA following CTA raised bias issues regarding the two domains “index test” and “flow and timing”. Overall, there were no applicability concerns.

DISCUSSION

Summary of review aims and key findings

This systematic review set out to evaluate the value of performing a DSA in CTA-negative PMSAH patients and compare CTA and DSA complication risks. Eighteen studies were included with a total cohort of 669 patients. Seven vascular abnormalities missed on initial CTA were identified on subsequent DSA, resulting in a conservative NPV of 99%. Complications following CTA and DSA were sparsely described, albeit at a risk of 0% and 1.35% respectively.

Imaging protocols

Our analysis is a contemporary pragmatic record which pooled data from multiple departments, using different types of CTA and DSA protocols. These were performed in several health care settings using primarily a unified definition of PMSAH suggesting that these data are widely applicable to the investigation of PMSAH patients.

There are however several cautions that need to be exercised in the interpretation of these results. Patients with a poor Hunt-Hess or the World Federation of Neurosurgical Societies' grade on presentation were excluded from our analysis. PMSAH is not only a radiological diagnosis and imaging findings need to be correlated to the clinical picture⁵; a poor admission status acts as an independent predictor of unfavourable outcome and warrants a management strategy similar to patients of an "aneurysmal" SAH.^{33 34} Of patients with appropriately defined PMSAH, a benign presenting status (GCS 15) was present in all, although a detailed breakdown was only reported in a few studies. The time between ictus and CT brain was also not well described in the studies reviewed; four studies provided details regarding the specific timing with about one fifth of patients missing the diagnostic window for PMSAH. SAH blood normally resorbs over time, and a scan at 3-days suggesting a PMSAH may well represent the residual blood from what was in fact a patient with diffuse SAH presenting in a delayed manner. We were unable to ascertain with the data available whether the delayed diagnoses

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were more prevalent in such patients, however we would argue that a more cautious approach should be exercised for patients scanned after 24 hours of ictus whose CT images demonstrate a perimesencephalic pattern of bleed. The diagnostic utility of CTA depends on its quality and personnel responsible for reporting. The DSA and CTA studies were all reported by a neuroradiologist, and most series confirmed their radiological findings by dual interpretation. CTA datasets are large and significant arterial pathology could be missed by a single reporter. Double reading reduces error rates, and if a move away from DSA is considered, it is not only critical that images are interpreted by experienced clinicians, but also that these images are independently assessed by two clinicians.³⁵ Another issue that should be highlighted is that for patients subject to DSA, a significant proportion were not getting 6-vessel imaging and complete diagnostic information. This is problematic since patients undergoing such invasive procedures are at risk of complications and if performed, should at least be to completeness.

Missed vascular abnormalities and DSA complications risk

We found that the probability of a DSA demonstrating any abnormality in CTA-negative PMSAH patients was approximately 10/1000. The probability of finding a macrovascular cause responsible for the haemorrhage as stated by the study authors was 7/1000. We also found that performing a DSA in PMSAH patients is not without risk and can result in serious adverse events in 14/1000 patients. If one applies one of the two miss rates against the risk of serious neurological complications identified in this study, these results suggest that DSA may not be required in patients with PMSAH, if the initial CTA is normal. The risk of DSA complications varies widely and depends on the timing of follow-up, the adopted definition and clinical setting. The risk of persistent neurological complications has been the primary focus of historic large-scale prospective studies which reported a pooled rate of approximately 0.1%.³⁶ More recent studies similarly report a low risk but show a non-negligible rate (~4-8%) of access-site hematoma, embolic stroke, pulmonary and cardiovascular complications and long term post-

procedural headache, which increases with age, comorbidity burden and performance of procedure in low patient-volume centres.^{8 37 38} These factors ought to be considered and conveyed to the patient; specifically, in an era of shared decision making. Economic analyses need to be also undertaken to specifically address the issue of patient transfers to specialist neuroscience units for further investigation and identification of a delayed diagnosis *versus* DSA-associated complications. Furthermore, the clinical relevance of a DSA picking up an abnormality initially missed on CTA needs to be further evaluated. Small irregularities in blood vessels, such as ‘arterial blebs’ or extremely small aneurysms may not warrant treatment, but nevertheless, could warrant radiological follow up.

Given the overall low incidence of vascular abnormalities on delayed invasive imaging in such patients, identification of risk factors of delayed diagnoses requires pooling of a large number of patients from multiple centres. Individual patient data were not available for use in analysis and therefore such inferences could not be made. Assessment of predisposing radiological and clinical features could help stratify diagnostic strategies; high-risk patients may require more comprehensive and early investigation as to facilitate early treatment of vascular abnormalities, if identified, whereas a negative high-quality CTA in low-risk patients with non-favourable DSA-related characteristics may suffice.

Comparisons to published systematic reviews

In agreement with our results, a recent meta-analysis investigating the utility of repeat imaging after initial negative CTA or DSA concluded that a repeat DSA is not required in patients with PMSAH.²³ Furthermore, another systematic review addressing the question of repeat imaging in patients with non-PMSAH stated that it is warranted. However, they highlighted the heterogeneity of imaging protocols, an issue replicated in this review of PMSAH patients.³⁹

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Study limitations

The analysis was based mainly on retrospective studies which were largely single centre. As a result, case ascertainment could not be guaranteed. PMSAH accounts for only 6-12% of all patients presenting with a SAH. If our CTA false-negative rate is correct, each large centre treating 100 patients with SAH each year is likely to miss a relevant abnormality in two PMSAH patients every 3 years. Given this infrequent rate of presentation, it is possible that not all adverse events and delayed diagnoses are identified by retrospective studies and the true risks might be misestimated.

CONCLUSIONS

In patients presenting within 72-hours of ictus with a PMSAH, as radiologically and clinically defined in this systematic review, an initial negative CTA may be sufficient in ruling out a cause for the haemorrhage and a subsequent DSA might not be required for most cases. DSA risk cannot be ignored and is likely under-reported but if opted for, patients should be appropriately counselled of the potential serious complications and the low probability of a vascular lesion being identified. Due to the poor evidence base comprising retrospective studies, the results of this review need to be validated by a large prospective multi-centre study with complete case ascertainment.

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DETAILS OF CONTRIBUTORS

M. Mohan: study idea conception, protocol development, data collection, data analysis and manuscript writing/drafting.

A.I. Islim: study idea conception, protocol development, data collection, data analysis and manuscript writing/drafting.

L. Dulhanty: study idea conception, protocol development and manuscript writing/drafting.

A. Parry-Jones: study idea conception, protocol development and manuscript writing/drafting.

H.C. Patel: study supervision, study idea conception, protocol development and manuscript writing/revision

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CONFLICTS OF INTEREST

The authors have no relevant disclosures to declare.

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None.

DATA SHARING

Study data are available upon request from the corresponding author.

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Figure legends

Figure 1. PRISMA flow chart demonstrating the study selection process

Confidential: For Review Only

PRISMA flow chart demonstrating the study selection process

58x49mm (300 x 300 DPI)

Online Supplementary Material

Online supplementary table 1. Search terms for Medline (Ovid) and Embase (Ovid)	
Date: 24/07/18	
Search	Query
#1	exp subarachnoid h?emorrhage/
#2	((perimesencephalic or pretruncal or non-aneurysmal or (CT* adj2 negative)) adj3 h?emorrhage).mp.
#3	1 and 2
#4	(DSA or digital subtraction angio* or CTA or computed tomography angio* or CT angio*).mp.
#5	3 and 4
#6	limit 5 to (English language and yr="2000 -Current")

Identifiers	Study_ID
	Patient_ID
Demographics and medical history	Age (mean)
	Sex
Presentation	Presenting GCS
	Hunt-Hess
	WFNS
CT brain	Time from ictus to CT brain/days
	Type of CT scanner
	Definition of PMH
	Who interpreted CT brain
	Single or double reporting
CTA brain	Time from ictus to CTA brain/days
	CTA protocol
	Who interpreted CTA brain
	CTA interpreted prior to DSA
	Single or double reporting
	Abnormality detected on CTA
	Abnormality detected further details
	Any CTA complications
	If so, what complications
	Time from ictus to FIRST DSA
First DSA	Time from CTA to FIRST DSA/days
	DSA unit
	DSA protocol
	Who performed/interpreted DSA
	Single or double reporting
	Abnormality detected on FIRST DSA
	Abnormality detected further details
	Any DSA complications
	If so, what complications
	Was a 2nd DSA performed
2nd DSA	Mean time from CTA to 2nd DSA/days
	Mean time from 1st DSA to 2nd DSA
	Abnormality picked up on 2nd or delayed DSA?
	Abnormality further details
	Any DSA complications
3rd DSA	If so, what complications
	Was a 3rd or delayed DSA performed
	Mean time from 2nd DSA to 3rd DSA
	Abnormality picked up on 2nd or delayed DSA?
	Abnormality further details
	Any DSA complications
	If so, what complications

Online supplementary figure 1. Data collection proforma

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Online supplementary figure 2. Quality assessment results